Volume 97 Number 1

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January 1979

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International Editorial Board

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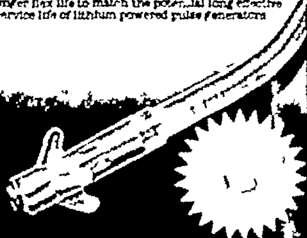
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[illegible]

Myocardial leads are [illegible] placement.

[illegible]

Warnings

[illegible]

March, 1979

American Heart Journal

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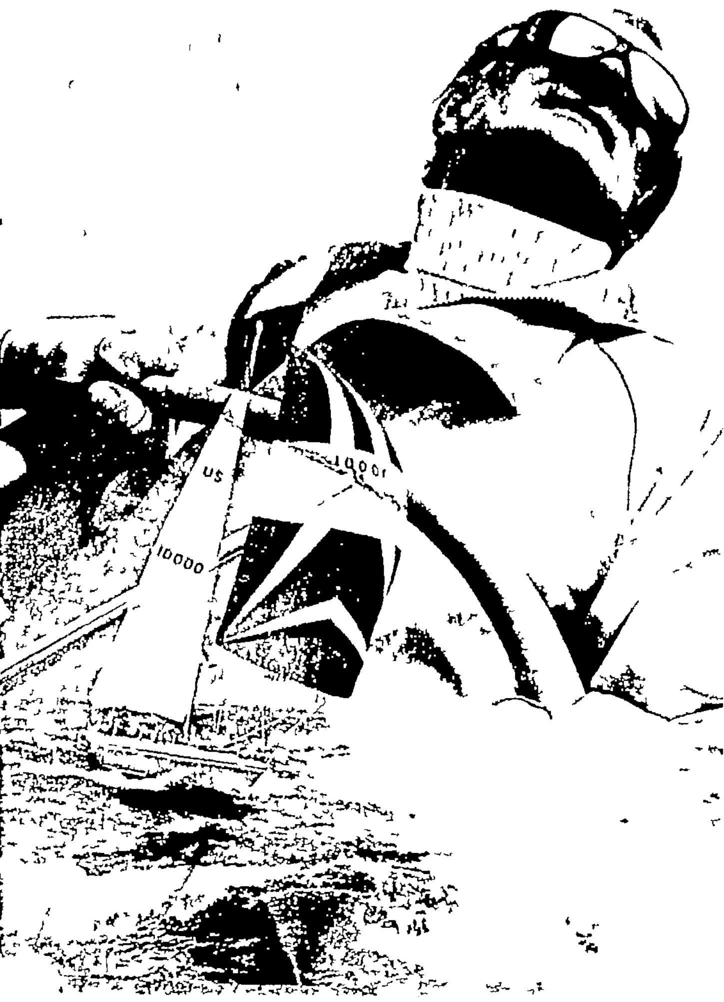
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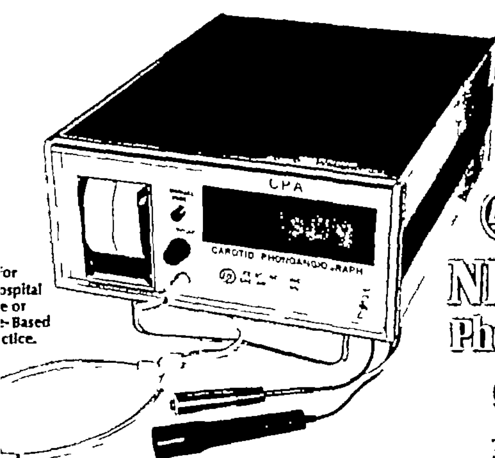
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NEW Recordin[g] Phonoangiograp[h]

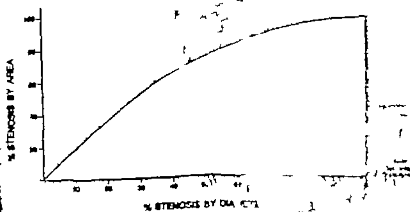
(CPA) for Cerebral Vascular evaluation

The major diagnostic CPA param[e]ters are absence or presence of 1s[t] and 2nd heart sounds, absence o[r] presence of high frequency conte[nt] in systole or systole and diastole and the differential character of t[he] three traces taken on each side

The sensitivity amplification quantitation and frequency rang[e] of CPA is well above the capacity of the human ear This allows appreciation of bruits that cannot b[e] heard with a stethoscope The advantages of quantitation and har[d] copy are obvious

CPA is helpful even for the experi[enced] examiner in identifying transmitted murmurs

% Stenosis By Area	DESCRIPTION	CPA TRACING
0-44	1) Normal 1st and 2nd heart sounds with no significant audiofrequency content [illegible] during either systole or diastole. [illegible] of only the 1st heart sound does not suggest abnormal carotid artery pathology	
44-64	2) The first heart sound is obliterated, high frequency content is noted at the initiation of systole. As the lesion becomes more severe the audiofrequency content extends over larger portion of systole	
64-96	3) The [illegible] and 2nd heart sounds are obliterated high frequency content is observed throughout systole and extends partially into diastole. As the lesion becomes more obstructive the audiofrequency content extends over larger portion of diastole	
96-100	4) When the lesion becomes severe enough to significantly reduce blood velocity, turbulence [illegible] reduced, and the abnormal audiofrequency content is lost. In this case the CPA tracings may be normal. In some patients the heart sound amplitude [illegible] reduced.	



Patient groups most often suggested for routine Cerebral Vascular Evaluation include:

a) Hospital admissions over 6[0] years of age
b) Patients undergoing cardiopulmonary bypass
c) Patients with multiple risk factors for arteriosclerotic disease

References bibliography and details on request.



Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S.A.
Tel. 203 869-2011

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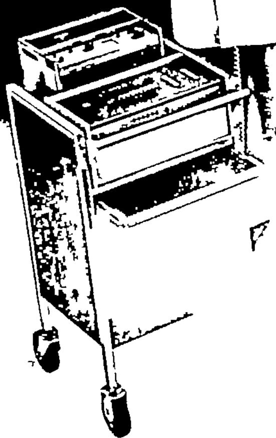
2 Fear of pain a major deterrent to achieving acceptable (and desirable) levels of activity including sex may be allayed with Cardilate Effective prophylaxis and improved exercise tolerance help toward normalizing the lives of [illegible] patients

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erythrityl [illegible]

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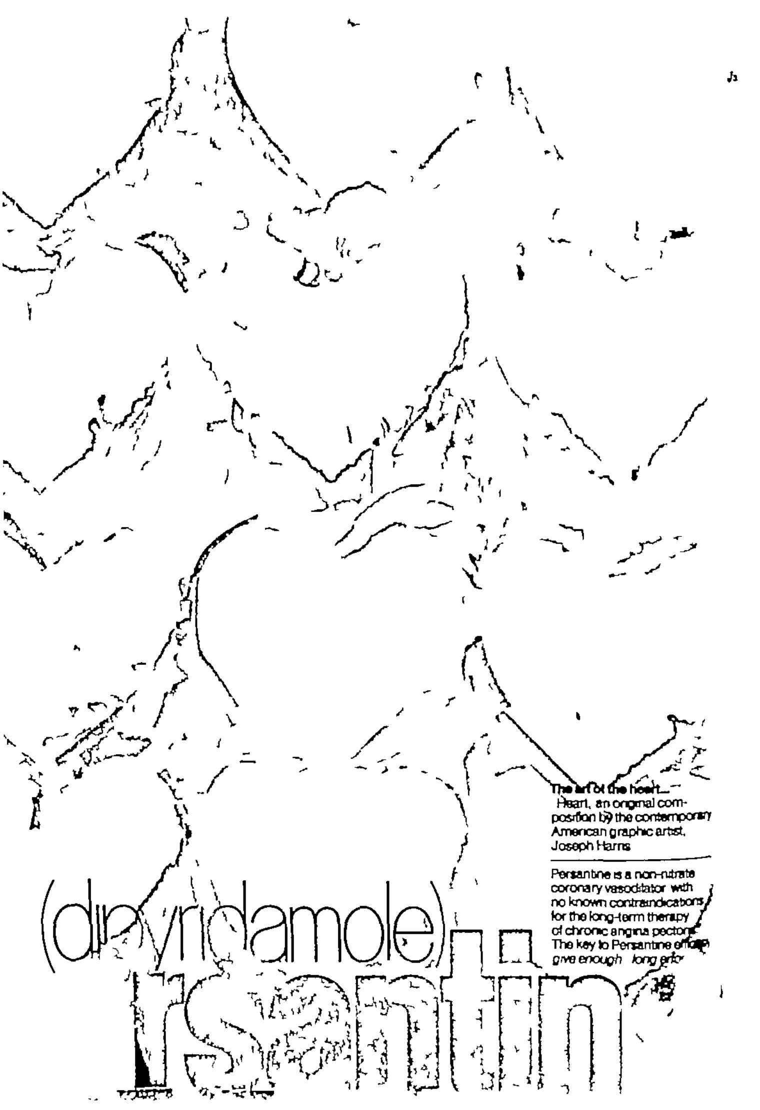
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(dipyridamole)
rsantin
The art of the heart...
Heart, an original com-
position by the contemporary
American graphic artist,
Joseph Harris
Persantine is a non-nitrate
coronary vasodilator with
no known contraindications
for the long-term therapy
of chronic angina pectoris
The key to Persantine
give enough long

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American Heart Journal

January 1979 Volume 97 Number 1

Editorial

Of conformists

G. E. Burch, M.D.
New Orleans, La.

It is easier to be a conformist, to be complacent and to accept everything as entirely correct than to question the validity of data, practices, edicts and programs. To be popular is desirable, but not if popularity is traded for truth, integrity, and honesty of opinion. Were we to accept all practices of 1977 as correct, never questioning them, and consider that a change is not needed and that there is little else to be done, then advancement would be arrested and errors promoted, so that 1977 and 2077 would not be different. To refrain from continually reviewing our state of knowledge critically, constructively, and in search of the truth would be unpardonably negligent. Science and medicine must be under constant critical review. But critical review must be directed at issues, only, and decisions made objectively and not emotionally nor with personal disrespect to anyone nor entirely for personal gain and self-aggrandizement. We must be forever free to speak openly on all issues, always avoiding personalities. To be denied the privilege of free, critical, and constructive thought is to be muzzled scientifically, and only truth suffers. Regardless, with time, truth shall eventually prevail, anyway. It is the obligation of everyone in medicine, research, and education to seek the truth and to insist on utmost quality in research and teaching at all times. There must be no compromise. No committee of men can establish an alternative by edict that will survive. *Bigness is not commensurate with greatness.*

There is too much duplication of research at present. There is so much more to do than to duplicate what has been done satisfactorily or established decades ago, even if the duplication and reconfirmation are achieved with more sophisticated methods. Modern sophisticated apparatus employed carelessly and poorly is certainly no substitute for less sophisticated apparatus used extremely well in the past.

Too many publications are non-critical reports of poor quality studies, and many are unnecessary. In too many instances the investigators are "grant managers" who are too busy with their managing to think creatively or profoundly. This situation, unfortunately, results in poorly trained "trainees"—a sort of "untraining program." Research is difficult, tedious, and time consuming. It requires freedom, solitude, and thought, all of which are difficult to obtain in a "frustrating" laboratory or clinic. Personal involvement, study, and discourse are absolutely necessary in research.

There has been an enormous change in medical research and education during the past 25 years. Surely, significant advancements have been made. But, unfortunately, much of the change has not been good. The funding of research and training in cardiology (and all of medicine as well) has not always been good or desirable. The psychic stress placed upon investigators, espe-

From the Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of Louisiana, New Orleans.

Supported by Grant HL-14[illegible] from the National Heart, Lung and Blood Institute of the United States Public Health Service, the Rowell A. Billups Fund for Research in Heart Disease, and the Feazel Laboratory.

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Reprint requests: George E. Burch, M.D., Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, La. 70112.

cially established investigators, has been extensive. It is not uncommon to find an "investigator" in a laboratory more concerned with procuring his next grant than with his research. The investigator too frequently "shifts" to where the money is, from cardiology to cancer, then to aging, or to some other aspect of medicine "popular" at the time. Good research cannot be done with personal satisfaction, interest, and security by out guessing a committee or by following the "money train." Research is serious and difficult. The investigator must be prepared to defend his data and position at all times, while given an opportunity to pursue his own ideas and interests. The responsibilities in good high quality research are demanding enough without the additional and ridiculous distractions, annoyances, and psychic stress associated with the procurement of financial support. The procurement of funds for capable and dedicated investigators is the responsibility of wise, dedicated, and energetic administrators who genuinely appreciate high quality research. This is not the responsibility of the investigator himself. His job is to do high quality research.

Repeated published errors in research and training must not be tolerated by colleagues and associates, but who is to judge? Time does decide. Surely all investigators and teachers must be accountable at all times. The investigators must be free from annoyances but under constant critical surveillance by the "scientific crowd"—the research and training crowd. All investigators are members of this "crowd." Remember, this scientific crowd does exist—not in any one place at any one time, but as a group of people dispersed widely in entirely different settings. Each investigator, being a member of the crowd, can be led by a self-selected or politically appointed leader or group. The leader's responsibility is great. And, the people of America and the world wish and expect great returns from this crowd of investigators. The crowd, like any crowd, is readily led by money and by those who control money. Wisdom, not money, should determine leadership.

The "crowd leader" concept may be acceptable to some extent, but never to the exclusion of the independent creative thinker and investigator whose research interest is different and unorthodox. The opinions or decisions of any crowd, even though dispersed and not unified in a small gathering in a single place at any one time, are highly emotional, non-critical, and not necessarily always right. A scientific problem can never be decided by a crowd or committee vote. We need only to think of Galileo, who was the only one independent of the crowd of his time. When he presented data indicating the earth was round and not flat, he was sentenced to death by the vote of the "scientific crowd" of his day, his peers. He was later pardoned of his scientific sacrilege, but he was correct and the crowd of peers was wrong. There must be a comfortable place for a free thinking investigator, even when or in spite of being a non-conformist, as long as he speaks and directs his attention and considerations to the issue and not to people. Great advancements in knowledge usually emanate from the mind and effort of a single person working alone and with freedom.

The conformist follows a path of little resistance, but in return for this policy he becomes a technologist and is destined to function, consciously or subconsciously, in cooperative efforts among widely dispersed laboratories. Conformists, as a rule, are not independent researchers and creative thinkers. Certainly all that prevails in education and research is not and cannot be right. However, for the non-conformist to question any results of the conformists is "antagonism" and "obstructionism" in the minds of the conformists. It is only through independent effort and thinking that the non-conformists can and will succeed. It is impossible to do research independently and in unknown fields and still conform completely. Freedom from inhibiting and dictated influences is of utmost importance to education and research. Conforming to assure "academic freedom" by means of politics, threats, and demonstrations provides only pseudo-academic freedom and jeopardizes true academic freedom.

"True academic freedom" must be spontaneous and real emotionally. It cannot be established or assured by fiat. Achievements acquired through political maneuvering, subtle or overt, are no achievements at all.

Fortunately, there is a place for the non-conformist and independent teacher, investigator, and thinker. The independent thinker engaged in venture research demands quality in research. He must be left alone to make significant advancements, so well exemplified by Mrs. Jocelyn Bell Burnell. Jocelyn Bell was a 19-year-old female

graduate student with perseverance and reliable high quality data She discovered the pulsars in the universe a discovery that is said to be the greatest discovery in astronomy during the past century Fortunately she was only a "mere" investigator who was left alone and undisturbed to study and "investigate, "research," and question with perseverance and the inquisitive thinking of a dedicated non-conformist. She had to overcome forces of conformists to have her great discovery about the universe finally accepted. The story of this recent discovery of pulsars by a graduate student is worth knowing and certainly admiring. This discovery by a non conformist, as most great discoveries, could not have been planned in advance—an unfortunate almost universal requirement of investigators these days.

Opportunities for absolute freedom in thought, study teaching, and research of the non-conformist must be developed and preserved. Unless this is done science and knowledge are unlikely to advance in a major way The great advancements in knowledge and the great discoveries have generally been the result of independent thinking and effort of little known investigators, so little known that they had difficulty providing for their own scientific existence. Einstein's mathematics and advancement in thinking are good examples. Had Einstein been a mathematical conformist, his advancements in knowledge would never have occurred. Nicolle Archimedes, Newton, Gauss, the Curies, Fleming, and Jocelyn Bell Burnell *represent only a few non-conformists in effort and thought.*

The conformist has little difficulties with his "peers, especially if his research and teaching philosophy conforms with theirs. The conformist has many peers, but the non-conformist has no peers. There are extremely few non-conformists in America. Should the non-conformist appear among the conformists, he is certain to encounter difficulties, even though his remarks and findings are limited to the issues and problems and not to personalities. The most charitable response the non-conformist may receive is, "he and his ideas are not orthodox. The significance of his ideas can only be finally determined by experiment, study and time. The non-conformist must never be ignored or chastized. Remember Galileo! Kreb's Nobel award winning studies had been rejected for publication by the reviewers of *Nature*. Newton's paper on optics was rejected for publication. Newton once said that to describe something new results in devoting one's entire lifetime to defending it. Many years later his classic book, *Optics*, appeared.

Who can decide in advance who is to make the great discoveries? Even the discoverer himself cannot.

The more people thinking about the problems of man and studying nature the greater is the likelihood that new great fundamental advancements in science and knowledge will be made. Those who have made the great discoveries were generally unknown until their announcements appeared. Again remember Jocelyn Bell Burnell! No one is to be discounted—not even a female graduate student.

The well known and highly supported conformists have not made great advancements in knowledge and probably never will. Their contributions are usually technologic. Those who provide the financial support for the conformist have little at stake—their time and effort usually involve not much more than the "stroke of a pen," and they usually dispense someone else's money anyway

The chance of attaining a significant discovery or advancement in knowledge would be greater if 20 or 30 investigators were supported per million dollars than if one investigator" received the million dollars. One hundred million dollars per year could support at least 2,000 creative thinkers and non-conformists and 2,000 different *approaches to the unknown. This would be no great* or expensive gamble these days. Large laboratories are necessary for expensive technologic developments, such as with NASA programs and putting a man on the moon. Surely many important spin-offs were developed from this program. But, what are the great *new* discoveries? The NASA program is an extensive, expensive, and wonderful application of existing knowledge. Such programs must not be sacrificed but they do not represent venture research and should not be supported at the expense of venture research. There is a great need for both.

The opinions, ideas, and publications of the non-conformist, like those of all human beings, are subject to error and must be defended by him. Nevertheless, he should at least be heard and seriously considered. Remember the "crowd is not necessarily always correct, and the fact that

they represent the majority does not make them right even in a democracy where the principle is that the majority rules. This principle may apply to politics, but it does not hold true in science And politics and science do not necessarily support each other or assure the best results or correct answers to the wonderful secrets of nature Most of the fundamental principles of nature are unknown and once displayed are usually found to be extremely simple and exciting to behold The non-conformist must be welcomed in the exciting adventures of studying the principles of nature but beware of the conformist The latter too often, is prone to be sycophantic and political, to the detriment of science research, scholarship and the pursuit of knowledge.

Too often committees are appointed because they conform to the opinions and objectives of the appointer Thus, new ideas and new approaches to science become unwelcomed. Conformists look upon venture research or unorthodox thinking with disdain and a certainty of early failure. But, who is a prophet who is to know the outcome? The need for tolerance and patience with the non-conformist is evident. He must be accepted and supported, at least modestly and left alone to work with total freedom, to think and to express himself He has something to contribute—something money cannot replace—his time and reputation and creative thinking.

I recommend the support of thousands of dedicated highly motivated investigators in relatively small laboratories engaged in the study of the unknown, but with high quality principles, methods, and disciplines of research. The non-conformists must be provided with personal security as well, so that they will be free of stresses from economic needs and thereby be free to think and to do venture research. Venture research by non conforming scientists will produce the great discoveries.

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Clinical communications

Influence of hemodialysis on electrocardiographic wave forms

Kyozo Ishikawa, M.D., F.A.C.C.
Toshihiko Nagasawa, M.D.
Hideyo Shimada, M.D.
Tokyo, Japan

Hemodialysis has made a major contribution to the treatment of chronic renal failure. It requires the surgical creation of an arteriovenous shunt. Hemodynamically, however, such an arteriovenous shunt causes volume overload of both the right and the left ventricles, and thus leads to dilatation and/or hypertrophy of both ventricles. The majority of patients with chronic renal failure display to a lesser or greater extent systemic hypertension. As a result, patients on hemodialysis tend to show left ventricular hypertrophy with or without dilatation. A good knowledge of the extent of the ventricular overload is thus vitally important for the patient's care on hemodialysis. In clinical situations, diagnosis of left ventricular hypertrophy is commonly made by electrocardiogram (ECG). The ECG findings for left ventricular hypertrophy focus mainly on the high amplitude of the QRS waves in the left precordial leads.

It has been reported that acute changes in QRS amplitude are observed in association with acute changes in venous return, in hematocrit value and in association with bleeding. Since hemodialysis causes marked hemodynamic alterations,[1-4] it can be reasonably supposed that hemodialysis will also cause such acute changes in the ECG as may lead to an erroneous diagnosis of left ventricular hypertrophy.

To permit critical evaluation of the ECGs of patients on hemodialysis, an attempt was therefore made in the present study to determine whether or not there was an acute alteration in the QRS amplitude due to hemodialysis.

Materials and methods

The study group consisted of 19 patients with chronic renal failure on hemodialysis. There were 14 males and 5 females, ranging in age from 16 to 70 years (mean 35 years). All the patients presented with moderate severity without evidence of congestive heart failure and pericardial effusion. The apparatus used for hemodialysis was a CD 1 coil type artificial kidney manufactured by Nikiso Co., Japan. The amount of fluid withdrawal by hemodialysis ranged from 700 to 3,000 mL, with a mean of 1,720 mL. Hemodialysis was performed two or three times a week depending on the severity of renal failure.

A Frank lead system was used, with chest electrodes placed in the fourth intercostal space. The ECGs were recorded on a Mingograf 62 recorder and also on frequency modulated magnetic tape. Details of the recording techniques have been reported previously. The scalar ECG and vectorcardiogram (VCG) were recorded immediately before and after hemodialysis.

All ECG measurements were performed manually. The details were as follows. The measurements from scalar leads X, Y, and Z included the amplitudes of the P, Q, R, S, and T waves and durations of the P and the QRS complex. For all QRS measurements, the PR segment served as the baseline at the level of the first deflection of the QRS complex. For the P wave, the TP segment was used as the baseline. The maximal vectors for the QRS and T loop were determined

From the Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan.
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Reprint requests: Dr. Kyozo Ishikawa, M.D., Kyorin University School of Medicine, 6-20 Shinkawa, Mitaka-City, Tokyo, Japan.

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Table I Electrocardiographic and echocardiographic findings before and after hemodialysis

Pt	Age	Sex	Weight (kg)		Rx (mV)		Ry (mV)		Rz (mV)		LVID (mm)		LVID (mm)	
			B	A	B	A	B	A	B	A	B	A	B	A
T.N	30	M	[illegible]8.5	55.0	1.100	1.150	1.723	[illegible]	1.200	1.175	–	–	–	–
T.Y	49	M	65.5	53.5	1.433	1.640	0.383	0.490	1.300	1.000	47	42	37	35
Y.I	47	F	41.5	40.	0.938	1.050	1.038	1.200	0.677	0.677	33	33	23	22
T.H	20	M	46.0	44.0	3.133	3.300	0.600	0.600	1.800	1.800	42	37	36	33
S.K	23	M	49.8	47.3	2.075	2.125	1.150	1.325	[illegible]	1.000	52	49	30	29
S.K	42	M	65.2	63.2	1.890	[illegible]500	0.800	0.950	0.870	0.925	61	31	49	29
S.M	39	F	44.8	44.0	1.333	1.600	0.883	1.060	1.117	1.350	47	42	33	34
N.I	60	M	72.6	69.5	1.433	1.517	[illegible]	0.850	0.900	0.800	36	31	22	20
T.T	45	M	61.7	60.6	1.390	1.900	1.390	1.600	0.640	0.700	46	45	37	33
A.N	30	F	43.0	41.5	1.278	1.850	1.425	1.750	0.875	1.000	50	47	40	39
M.T	34	M	54.5	51.5	2.167	2.900	1.200	1.350	1.200	1.650	4[illegible]	43	37	37
A.M	30	M	52.8	50.6	2.167	3.150	1.400	1.950	1.933	[illegible]	53	46	39	35
M.E	39	F	56.0	54.2	1.567	2.300	1.400	2.050	[illegible]033	2.450	49	43	37	33
M.T	34	M	53.2	50.3	2.167	2.800	1.200	1.300	0.900	1.350	53	45	42	40
M.T	27	M	63.0	61.7	1.650	1.650	1.575	1.500	1.200	1.575	55	50	35	33
J.T	18	F	47.5	46.8	0.983	1.150	0.767	0.883	1.200	1.400	46	28	38	30
T.K	30	M	44.8	44.1	2.500	3.200	1.500	1.800	1.100	1.400	45	42	37	37
K.G	70	M	45.2	44.5	0.438	0.613	0.813	0.838	0.950	1.175	–	–	–	–
M.K	30	M	53.5	51.2	2.633	3.000	1.800	2.[illegible]0	[illegible]133	2.700	52	47	41	30
Mean	35		51.9	50.1	1.693	2.071	1.147	1.252	1.198	1.436	47.1	41.9	36.2	33.2
SD			7.4	6.9	0.637	0.823	0.297	0.518	0.463	0.581	6.9	6.00	6.34	6.7[illegible]
p value (two-sided sign test)			0.01		0.01		0.01		0.01		0.01		N.S.	

B = before hemodialysis, A = after hemodialysis.

in three plane projections—frontal, left sagittal and horizontal.

Since respiration is the most important physiological variable causing beat-to-beat variations, seven consecutive heart beats were selected from each record so as to include at least one respiratory cycle. A mean value for each ECG measurement calculated from the seven consecutive beats, was used for the analysis. Chest x rays and echocardiograms were also taken, and the hematocrit and serum electrolytes including K, Ca, and Mg, were measured before and after hemodialysis. The echocardiograms were used to measure the internal dimensions of the left and right ventricles, and also to estimate whether pericardial effusion might exist. Echocardiographic studies were carried out with a Toshiba SSL 51U using a 10 mm. diameter 2.25 MHz transducer focussed at 7.5 cm. The echocardiograms were recorded on a Toshiba SSL 51U strip chart. The patients were studied in the supine or left lateral decubitus position. The transducer was placed in the standard position, usually at the left fourth intercostal space lateral to the sternal margin. An M mode scan was then performed from the aortic root to the apex of the left ventricle. The standard ECG (Lead II) was simultaneously recorded on the echocardiogram. The hematocrit value was measured, since it can be an index of the electrical resistivity of the intracavitary blood mass, which is considered to influence the body surface potentials.

Results

Table I summarizes all pertinent data obtained before and after hemodialysis. As shown in the table and in Fig. 1, the amplitude of the R wave in Leads X, Y and Z, the sum of the R wave amplitudes of the three leads (Rx + Ry + Rz) and the magnitudes of the maximal QRS vector in the three planes, were significantly augmented after hemodialysis.

Fig. 2 shows averaged scalar leads and vector loops before and after hemodialysis. These were obtained by plotting the mean values of eight equally divided points of the QRS wave. The figure clearly reveals a marked increase in the magnitudes of the R waves in the three leads and of the QRS loops in the three planes, after hemodialysis.

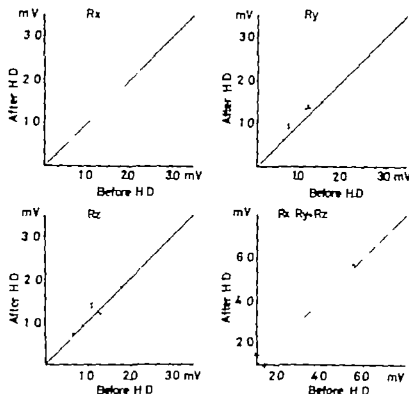


Fig. 1 Comparison between the R waves in Leads X,Y and Z before and after hemodialysis. Not that the R waves in the three leads, and the sum of the R waves in the three leads, were augmented after hemodialysis.

Fig. 3 shows a representative ECG in which the R wave amplitudes in Leads X,Y and Z were increased from 1 70, 0.80 and 0.86 mV before hemodialysis to 2.50, 0.95 and 0.93 mV after hemodialysis, respectively

Fig 4 gives a VCG recording for the same patient as in Fig. 3 in which the magnitudes of the maximal QRS vectors in the frontal, sagittal, and transverse planes were increased from 1.88, 0.86, and 1 79 mV before hemodialysis to 2.57 1.00, and 2.50 mV after hemodialysis, respective ly None of the patients in this study displayed clinical or echocardiographic evidence of pericar dial effusion before and after hemodialysis. The internal dimension of the left ventricle in diastole tended to be smaller after hemodialysis, whereas no significant change was observed in the internal dimension in systole. No patient revealed an increase in the left ventricular dimension after hemodialysis.

Fig. 5 shows echocardiograms obtained from the same patient as in Figs. 3 and 4 in which no pericardial effusion was observed and the internal dimensions of the left ventricle in systole and diastole were 51 and 48 mm. before hemodialysis, and 31 and 29 mm. after hemodialysis, respective ly The mean hematocrit value showed a slight increase from 28 per cent before hemodialysis to 32 per cent after hemodialysis. The mean value of serum potassium decreased from 5.8 mEq /L. before hemodialysis to 3.5 mEq /L. after hemodi alysis. Serum Ca and Mg showed no significant changes due to hemodialysis.

Discussion

The major ECG change induced by hemodialy sis was the significant increase in the magnitudes of the R waves in Leads X,Y and Z, and in the magnitudes of the maximal QRS vectors in the frontal sagittal, and transverse planes. Although the present number of cases was small the constancy of the described findings in all cases appears to be significant. Del Greco and asso ciates revealed that blood volume was consider ably reduced after hemodialysis and this may be attributable to a decrease in plasma volume Manoach and co-workers reported that an acute reduction in the circulating blood volume due to hemorrhage resulted in a reduction of the precor dial QRS amplitude.

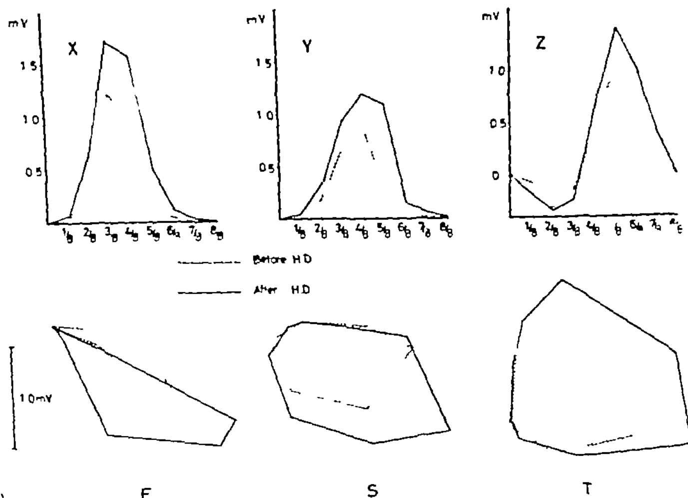


Fig 2. Averaged scalar leads and vectorcardiographic plane projections based on 19 records obtained from patients on hemodialysis. The QRS complexes were normalized in time by dividing the duration int eight equal parts. Thus, each point represents ⅛, ²⁄₈, ³⁄₈, ⁴⁄₈, ⁵⁄₈, ⁶⁄₈, ⁷⁄₈, and ⁸⁄₈ of the QRS. Note that the R amplitudes in the three leads and the magnitudes of the maximal QRS vectors were markedly increased after hemodialysis.

Angelakos and Gokkan also observed a reduction in the magnitude of the QRS potentials by superior and/or inferior vena cava occlusion in the dog. It thus appears quite reasonable to speculate that the reduction in circulating blood volume caused by hemodialysis might exert such an effect as to reduce the QRS voltage. However this is quite contrary to the results of the present study.

Pericardiocentesis in a patient with pericardial effusion usually leads to an increase in the QRS amplitude on the body surface. If the patients used in this study had shown pericardial effusion, it would have been quite natural to consider that hemodialysis reduced the extent of pericardial effusion and consequently increased the body surface potential. However no evidence of pericardial effusion could be demonstrated in our patients by echocardiograms or chest x-ray examinations. It thus appears less likely, though not entirely impossible, that a reduction in the amount of pre-existing pericardial effusion through hemodialysis was responsbile for the decreases in magnitude of the above-mentioned ECG and VCG parameters. Nevertheless, it is also feasible that the echocardiograms were unable to detect the presence of pericardial effusion, although echocardiograms are known to be quite sensitive even to small amounts of pericardial effusion. Whether or not such a small, almost imperceptible amount of pericardial effusion could exert any significant influence on the QRS amplitude on the body surface has yet to be clarified.

It has been reported by several investigators that an acute change in hematocrit causes a marked alteration in the body surface potentials. However no essential change in hemato-

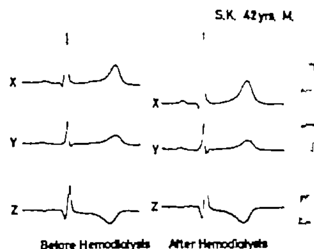
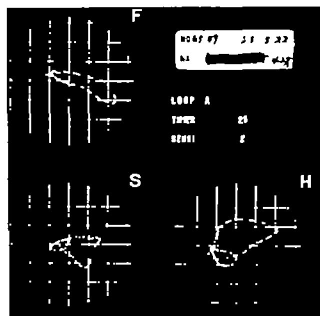


Fig. 3 Representative electrocardiograms obtained from 42-year-old man. The amplitudes of the R wave in Leads X, Y and Z were increased from 1.70, 0.80, and 0.86 mV before hemodialysis to 2.50, 0.95, and 0.83 mV after hemodialysis, respectively

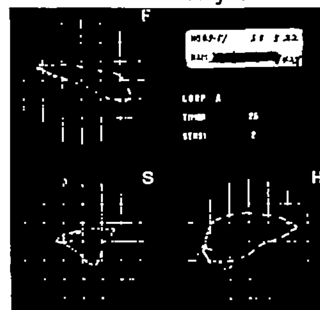
crit due to hemodialysis was observed in the present study

Bayley and Berry[11] have investigated the changes in body surface potentials caused by alterations in resistivity in different compartments of a nonhomogeneous conductivity model. They divided the torso model into the following seven different compartments heart-cavity blood, heart-wall region, pericardial environment, lung region muscle bone region, skin pad region and exterior medium. Each compartment has a different resistivity They showed that an increase in the resistivity of the intracavitary blood mass, the pericardium and the lung region caused a decrease in the body surface potentials. Unfortunately they were unable to show that a change in the resistivity of the heart-wall region would affect the body surface potentials, due to the intrinsic complexity

As discussed earlier there appears to be no essential alteration in the resistivity of the heart-cavity blood and the pericardium due to hemodialysis. From the viewpoint of the electrical resistance network of the thorax, it could therefore be reasonably assumed that the most remarkable changes would occur in the resistivity of the myocardium and the lung tissues. If the resistivity of the myocardium and the lung tissues were greatly decreased by hemodialysis, an increase in the QRS amplitude after hemodialysis could be readily explained. To our knowledge however there has unfortunately been no report so far to indicate such a reduction in the resistivity of the myocardium and the lung due to hemodialysis.



Before Hemodialysis



After Hemodialysis

Fig. 4. Representative vectorcardiographic plane projections obtained from the same patient as in *Fig. 3*. Note that the magnitudes of the maximal QRS vectors in the frontal, sagittal, and transverse planes increased from 1.86, 0.86, and 1.79 mV before hemodialysis to 2.50, 1.00, and 2.50 mV after hemodialysis, respectively

In the present study the internal dimension of the left ventricle in diastole tended to be somewhat smaller after hemodialysis. In other words, the intraventricular blood volume te

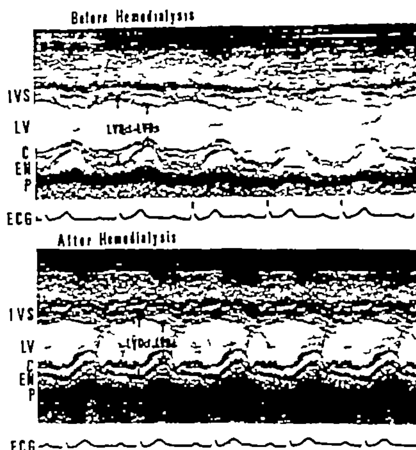


Fig 5 Echocardiograms obtained from the same patient as in *Figs. 3 and 4* Not that pericardial ffusion w observed nd that the internal dimension of the left ventricle in systole nd diastole decreased from 51 and 45 mm. before hemodialysis t 31 and 29 mm. after hemodialysis, respectively

decrease after hemodialysis. If one considers the effect of the volume of blood on the dipolar activation fronts existing in the left ventricle it is not surprising that an augmentation in the exter nal electrical field would be related to a decrease in volume. As the intraventricular volume decreases, the internal surface of the left ventricle decreases, thus allowing fewer units to have the highly conductive blood as the adjacent medium on at least one side This will cause a decrease in internal current flow which will have the effect of short-circuiting some of the electrical field and hence increasing the external field. It can thus be reasonably expected that decreased intracavitary blood volume due to hemodialysis will increase the QRS voltage by a short-circuiting effect Our hypothesis that the QRS voltage is increased by a decreased intracavitary blood mass agrees with the results of our previous study on ECG changes due to cardiac enlargement in patients with congestive heart failure, in which an increase in the spatial magnitude of the QRS vectors was always accompanied by a decrease in cardiac shadow *This hypothesis is also substantiated by* the recent report of Talbot and associates in which the maximum spatial QRS voltage in patients without left ventricular hypertrophy was inversely correlated with end-diastolic volume However the hypothesis remains speculative and elucidation of the true mechanism responsible for the observed phenomena must await further research.

It is hoped that the present report of an increase in spatial QRS voltage after hemodialy sis will serve to draw attention to this field and also provoke fresh thought regarding the underly ing etiology

Finally it should be emphasized that a sudden increase in QRS amplitude after hemodialysis might lead to an erroneous diagnosis of left ventricular hypertrophy Constant awareness of such voltage increases should thus be kept when ECGs from patients who undergo hemodialysis are examined.

Summary

Alterations in Frank lead electrocardiograms induced by hemodialysis were investigated in 19 patients with chronic renal failure. The most prominent findings after hemodialysis were marked increases in the magnitudes of the R wave in Leads X, Y, and Z, and of the maximal QRS vectors in the frontal, sagittal, and transverse planes. Echocardiographic and roentgenographic examinations revealed no evidence of pericardial effusion before and after hemodialysis.

Although the true origin of these findings remains undetermined, it appears reasonable to speculate that the decreased intracavitary blood volume due to hemodialysis may cause an increase in the QRS voltage by a short-circuiting effect. It should be emphasized that a sudden increase in QRS amplitude after hemodialysis might lead to an erroneous diagnosis of left ventricular hypertrophy. The clinician should be aware of such voltage increases when examining the ECGs of patients who undergo hemodialysis.

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Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment

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In recent years increasing attention has been paid to the urinary magnesium losses that accompany treatment with most diuretics. [..] In human experimental magnesium deficiency some authors have been able to demonstrate a concomitant potassium deficiency. These observations have been supported by animal experiments.[..] Nevertheless, the usual supplementation with diuretics is potassium alone.

This study was performed to investigate

1. Whether in patients suspected of having a magnesium deficiency the cellular potassium content can be raised with potassium supplementation alone.

2. Whether magnesium infusions have any influence on the cellular potassium content in these patients.

3. Whether there is any change in the frequency of ventricular ectopic beats (VEBs) after potassium infusions.

4. Whether there is any change in the frequency of VEBs after magnesium infusions in these patients.

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Material

The material consists of 34 patients, 14 males and 20 females, with a mean age of 68.1 ± 8.4 and 73.6 ± 9.0 years, respectively. 20 patients (six men and 14 women) suffered from congestive heart failure (CHF) with basal pulmonary râles and apical vascular enlargement on chest x-ray and 13 (six men and seven women) were being treated for arterial hypertension (AHT). All the patients with CHF and AHT were receiving diuretics, and six of them were hypokalemic. Finally one patient had a diagnosis of alcoholism and was not receiving diuretics; this patient was hypokalemic.

Twenty-four patients had a s-creatinine value ≤120 µmol/L., 10 patients had a value between 121 and 200 µmol/L.

Twenty-one of the patients were being treated with digitalis. Of the 33 patients receiving diuretics, 19 were on furosemide, 12 on thiazides, and two on a combination of these. Three patients had been treated for less than 3 months, eight for between 3 months and 3 years, and 22 for more than 3 years.

Methods

The patients were divided arbitrarily into three groups, I, II, and III. Group I consisted of nine patients, three with CHF and six with AHT. After an initial muscle biopsy, simultaneous blood sampling and a 3-hour ECG tape recording, the patients were given 30 mmol. magnesium sulphate intravenously in Ringer solution over approximately 10 hours. After a further 12 hours

Table I Mean electrolyte values ±1 S.D in serum (K/s, Mg/s) muscle (K/m Mg/m) intracellularly (K/i) and water (H_2O/m, H_2O/i) for Groups I and II before and after magnesium infusion and for Group II after a successive potassium infusion Serum values in mmol/L., muscle values in mmol/100 g FFDS and water in g/100 g FFDS K/i in mmol/kg. i.c water

	K/s	Mg/s	K/m	Mg/m	H_2O/m	K/i	H_2O/i
On admission	3.96 ± 0.43	0.80 ± 0.13	30.0 ± 5.90	4.02 ± 0.38	429 ± 58	153 ± [illegible]	256 ± 45
After Mg infusion	4.01 ± 0.43	1.40 ± 0.32	42.[illegible] ± 4.8[illegible]	4.00 ± 0.53	422 ± 49	154 ± 24	[illegible]1 ± 34
After K infusion	4.39 ± 0.50	0.96 ± 0.18	40.1 ± 5.23	3.9[illegible] ± 0.36	437 ± 36	154 ± 11	255 ± 35

Table II Mean electrolyte values ±1 S.D in serum (K/s, Mg/s) muscle (K/m, Mg/m) intracellularly (K/i) and water (H_2O/m H_2O/i) for Group III before and after potassium infusion and magnesium infusion

	K/s	Mg/s	K/m	Mg/m	H_2O/m	K/i	H_2O/i
On admission	3.72 ± 0.56	0.78 ± 0.18	39.5 ± 5.83	3.80 ± 0.35	422 ± 71	150 ± 4.7	260 ± 39
After K infusion	4.33 ± 0.53	0.77 ± 0.17	36.0 ± 4.77	3.81 ± 0.45	424 ± 58	150 ± 16	235 ± 41
After Mg infusion	3.97 ± 0.38	1.35 ± 0.34	42.3 ± 2.[illegible]	4.08 ± 0.33	408 ± 51	15[illegible] ± 10	266 ± 22

Amounts in the same units as in Table I

or so, a new muscle biopsy a new set of blood samples, and a new 3-hour ECG tape recording were obtained.

Group II contained 13 patients, 10 of whom suffered from CHF and three from AHT These patients were treated initially exactly as Group I but were subsequently given an intravenous infusion of 40 mmol. potassium chloride in Ringer solution over 10 hours. Twelve hours afterwards a third muscle biopsy and a third set of blood samples were obtained plus a third 3-hour ECG tape recording.

Group III consisted of 12 patients, seven with a diagnosis of CHF four with AHT and one patient with alcoholism. These patients were treated like the patients in Group II but the order of infusions was switched and consequently they started with the magnesium sulphate infusion.

Muscle biopsies were obtained by the method elaborated by Bergstrom i.e by a percutaneous needle biopsy from the lateral portion of the quadriceps femoris muscle, 15 to 20 cm. proximal to the knee. The muscle biopsies, 40 to 80 mg. wet weight, were rapidly dissected free from all visible connective tissue and fat and were rolled on a piece of quartz glass to remove all traces of blood. The muscle tissue was then attached to a preweighed platinum hook and repeatedly weighed on a Cahn 4700 electrobalance. The original wet weight was obtained by extrapolation to zero time The platinum hook with adhering muscle tissue was then placed in an oven at 110° C until constant weight to obtain the dry weight and the water content of the specimen. Fat was then extracted with redistilled petroleum ether After a new drying period the fat free dry solid weight (FFDS) was obtained.

The muscle tissue was then wet ashed in 1 N nitric acid and the electrolytes were determined by atomic absorption spectrophotometry in the solution left, according to the methods of Bergström and colleagues. Chloride was determined by atomic absorption spectrophotometry after precipitation with silver nitrate The intracellular electrolyte concentrations were determined according to the chloride method,[13] assuming chloride is freely diffusible across the cell membrane A normal resting membrane potential of 87.2 mV was assumed

Serum electrolytes were determined by flame photometry (Na, K) atomic absorption spectrophotometry (Mg) autoanalyzer technique (total carbonate and s-creatinine) and by titration with silver nitrate (Cl) Protein was determined by the biuret method. Digitalis concentration was determined by radioimmunoassay method.

The ECG tapes were read by one of the authors, not knowing the sequence of the infusions or the results of the muscle biopsies. VEBs

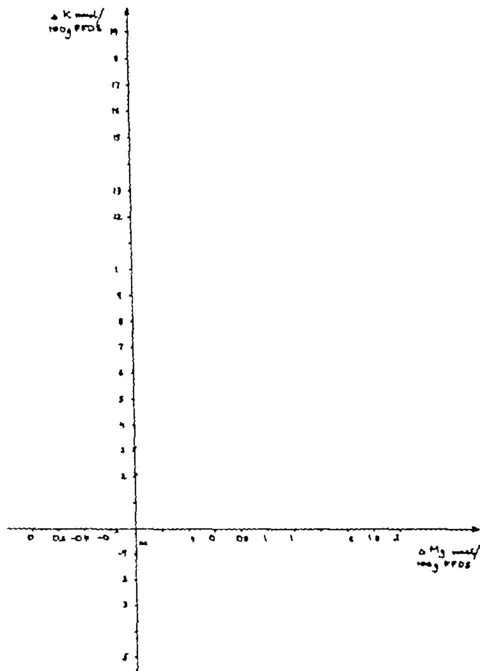


Fig. 1 Relation between changes in muscle magnesium content (Δ *Mg*) and changes in muscle potassium content (Δ *K*) after magnesium infusion. = 0.71.

were defined as QRS complexes coming too early with a duration exceeding 0.10 sec., without a preceding P wave, and with a configuration differing from the usual QRS complexes. To classify the VEBs further the traditional classification of Lown and associates was used.

Paired t statistics were used to compare the electrolyte and water values before and after the infusions of potassium and magnesium, as well as for comparing the frequency of VEBs before and after the infusions.

Results

Table I shows the Group I + II serum levels for potassium (K/s) and magnesium (Mg/s) in mmol/L as well as the muscle content of these ions (K/m and Mg/m respectively) in mmol and water (H_2O/m) and intracellular water (H_2O/i) in

g per 100 g FFDS. The intracellular concentration of potassium per kilogram intracellular water is also shown (K/i). The values are given on admission, after magnesium infusion, and after potassium infusion.

After magnesium infusion K/s had not changed significantly, neither had K/i. K/m, however, showed a significant increase ($t = 3.35$, $p < 0.01$). Mg/s showed an increase, but Mg/m had not changed significantly. H_2O/m and H_2O/i were also unchanged.

Following the potassium infusion, which was given to 13 of the 22 patients (Group II), there was a substantial increase in K/s. K/m showed a decrease, but not significant. The other parameters were unchanged statistically.

Table II shows the same parameters as Table I but for Group III. There was a large increase in K/s after potassium infusion. K/i was unchanged but K/m had actually decreased after the potassium infusion, though not significantly ($t = 2.12$, $0.10 < p < 0.05$). Mg/s had not changed significantly, neither had H_2O/m or H_2O/i. Mg/m showed a significant decrease ($t = 3.46$, $p < 0.01$).

After the magnesium infusion there was a large increase in Mg/s, but Mg/m too was higher ($t = 3.12$, $p < 0.01$). K/i had increased, but not significantly. However, a significant increase was found in K/m ($t = 3.75$, $p < 0.01$). K/s showed a significant decrease ($t = 2.24$, $p < 0.05$). H_2O/m and H_2O/i had not changed significantly.

The muscle sodium content (Na/m) did not change in the whole material after potassium infusion ($n = 25$, $t = 1.93$, n.s.). But after magnesium infusions there was a highly significant decrease in Na/m concomitant with the increase in K/m ($n = 34$, $t = 3.57$, $p < 0.01$).

Table III shows the frequency of VEBs per hour for Groups I + II. After magnesium infusion there was a significant decrease in the frequency of VEBs. This decrease paralleled the increase in muscle potassium content observed after magnesium infusion ($t = 4.38$, $p < 0.001$). Following potassium infusion there was no further change in the frequency of VEBs.

Table IV shows the frequency of VEBs per hour for Group III. After potassium infusion there was no change in the frequency of VEBs. Here, too, there was a significant decrease in the frequency of VEBs after magnesium infusion again in parallel with the increase in K/m ($t = 3.56$, $p < 0.01$).

Table III Number of ventricular ectopic beats (VEBs) before and after magnesium and potassium infusions in Groups I and II

Patient no.	*No. of VEB on admission per hr*	*No. of VEBs after Mg infusion per hr*	*No. of VEBs after K infusion per hr*
1	600	100	250
2	150	4	4
3	1800	1200	1390
4	0	0	0
5	7700	1700	300
6	350	0	0
7	4	7	80
8	190	20	30
9	1200	30	30
10	1200	850	150
11	900	100	50
12	90	60	10
13	20	20	40
14	0	0	
15	30	0	
16	670	60	
17	250	2	
18	250	150	
19	40	4	
20	450	300	
21	200	0	
22	450	80	

In the total material there was a highly significant decrease in the frequency of VEBs after magnesium infusion, from 392 to 146 per hour ($t = 4.72$, $p < 0.001$).

Discussion

In our investigation it is clear that potassium infusion did not result in any increase in muscle potassium content. On the contrary, K/m decreased after potassium infusion. This is in contrast to the concomitant rise in K/s after potassium infusion. The reason for this discrepancy may be a cellular magnesium deficiency. It has been shown that treatment with most diuretics induces an increased loss of magnesium in the urine.[28] As all but one of our patients were being treated with diuretics, there may have been a cellular magnesium deficiency.

Magnesium is a necessary activator of Na-K ATP-ase[11] which in turn supplies the energy required for electrolyte transport across the cell

[illegible table caption]

[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]

These findings [illegible] for [illegible] the intracellular potassium [illegible]. This view is also strengthened [illegible] earlier experiments and [illegible] magnesium [illegible] malnourished Jamaican children [illegible] lowered muscle potassium [illegible] levels [illegible] decrease in total [illegible] potassium in three magnesium deficient [illegible] induced magnesium deficiency [illegible] patients he observed that the total exchangeable potassium (TEK) fell during the period of [illegible] and could not be restored by potassium supplementation. Magnesium repletion however was associated with increased TEK even though the potassium intake was the same as before. Finally Caddell and Olsen in 1973 showed a concurrent magnesium and potassium depletion in malnourished Thai children.

Several animal experiments have demonstrated that a dietary deprivation of magnesium is accompanied by muscle potassium deficits despite an abundant supply of potassium. The muscle potassium deficiency could not be corrected unless magnesium was supplied.

The magnesium ion has been reported to influence the activity of the heart in some studies. The exact mechanism for this action has not been demonstrated as yet. One theory concerns the action of magnesium on Na K ATP-ase. A magnesium deficiency should then lead to a cellular loss of potassium and eventually to a lowering of the intracellular potassium concentration with a normal serum potassium level. As the resting membrane potential (RMP) is dependent largely on the ratio between intracellular and extracellular potassium, a lowering of only one of these parameters, with the other unchanged, would mean a change in RMP

$$E = -61.5 \log \frac{K/ic}{K/ec}$$

A lowering of K/ic leads to a less negative RMP i.e., the RMP of the cell approaches the threshold of excitation and consequently the cell is more easily excited.

The findings in our study agree with this theory i.e., an influence on potassium metabolism by magnesium. The magnesium infusions led to an increase in muscle potassium content and

although the intracellular potassium concentration did not rise significantly there was a decrease in the frequency of VEBs.

In conclusion, our study demonstrates that potassium infusion to our patients on long term diuretic treatment did not result in any increase in cellular potassium content neither did it influence the frequency of VEBs. In contrast to this, magnesium infusions led to a rise in cellular potassium content and a concomitant decrease in the frequency of VEBs.

Potassium supplementation to patients on long-term diuretic treatment does not seem to be adequate to keep the intracellular potassium content unchanged when a magnesium deficiency has developed. The time for this development varies, probably for several reasons, e.g., dosage and type of diuretic treatment nutritional intake of magnesium, a concomitant alcoholism or a secondary aldosteronism Such a state of magnesium deficiency and secondary cellular potassium deficiency is very difficult to detect as the serum magnesium level is not a reliable guide to the cellular magnesium content Also the serum potassium level is usually normal when there is a cellular potassium deficiency secondary to magnesium deficiency

In recent years some studies have demonstrated an increased frequency of VEBs in patients with hypertension and in patients with left heart failure. [8] These patients have been shown to run an increased risk of sudden death. One may speculate whether these patients have died from arrhythmias and whether this is the effect of an intracellular potassium deficiency secondary to magnesium deficiency on account of diuretic treatment.

Summary

Thirty four patients suspected of being magnesium deficient were given intravenous infusions of potassium and magnesium. The muscle contents of sodium, potassium, magnesium, and chloride were determined by atomic absorption spectrophotometry on skeletal muscle samples obtained by percutaneous biopsies. The frequency of ventricular etopic beats (VEBs) was assessed from a 3-hour ECG tape recording before the infusions and after the completion of each infusion. The potassium infusions did not result in any changes in the cellular potassium content, nor in the frequency of VEBs. After the magnesium infusions, however a significant increase was noted in the cellular potassium content and likewise a significant decrease in the frequency of VEBs. This emphasizes the importance of magnesium in potassium metabolism.

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4 No history of a recent myocardial infarction.

5. His bundle studies which were either normal or demonstrated only H V prolongation

The patients were categorized according to the New York Heart Association Classification. A similar rating system was used for the patients general medical condition, so that a patient with terminal carcinoma would receive a general medical Class IV even if the heart disease were trivial.

Bundle of His studies were done using multipolar leads and conventional techniques. The patients were studied in the catheterization laboratory in the post-absorptive state. Recordings were made using an Electronics for Medicine DR12 or a Mingograf† 803 recorder at a paper speed of 100 or 200 mm. per second. The H V interval was measured from the onset of the His bundle potential to the initial ventricular deflection, wherever it appeared first on the intracardiac or peripheral leads. Incremental rapid atrial pacing was used in assessment of atrioventricular conduction. Sinus node recovery times were performed using our previously published techniques and sinoatrial conduction times were analyzed Patients were included in the study when sinus node function tests, atrioventricular node conduction times (A H interval) and responses to atrial pacing were normal by published criteria and unpublished normal ranges used in our laboratory The authors performed all the His bundle studies and accumulated the follow up data

Among the 35 patients with an H V interval ≥ 60 msec., 18 received a permanent ventricular pacemaker (Long H V Paced Group) while 17 patients remained unpaced (Long H V Unpaced Group) The decision to implant a permanent pacemaker was left to the discretion of the private cardiologist.

Of the 24 patients whose H V interval was < 55 msec., two were immediately lost to follow up while four received permanent pacers at the urging of their private physicians These six patients were then removed from further analysis The 18 remaining constituted the Normal H V Group

Patients who received permanent pacemakers were followed by the authors in the Pacemaker Center at M[illegible] hore Hospital and Medical Center Pati[illegible] without pacemakers were followed by th[illegible] te physicians and each living patient wa[illegible] d and interviewed by the authors. F[illegible] tients who died the hospital records w[illegible] d and the patient's family and phy[illegible] interviewed to ascertain the mode of [illegible] dden death was defined as unexpect[illegible] ccurring *within minutes* of any symp[illegible] den death unrelated to chest pain sympt[illegible] gestive of a stroke or trauma, were con[illegible] xplainable by heart block, although [illegible] such as ventricular fibrillation [illegible] be excluded. In this study the foll[illegible] ceased when an unpaced patient de[illegible] documented progression to advanced heart block or died Except for Table II the term DP [illegible] defined as documented progression to advanced heart block requiring pacemaker implantation *in a previously unpaced patient* Follow up of paced patients was terminated only when the patient died. Because progression to heart block may lead to syncope or death, patients who had DP or who died were analyzed together Progression to heart block in patients with pacers was considered an incidental finding since the pacer protected them from the risks associated with DP in the unpaced. The number of patients in the Long H V Unpaced Group who remained stable (alive without DP) was compared to the number remaining stable (alive) in the Normal H V and Long H V Paced Groups. Data were compared using the Student's t test Yates Chi-square test and Fisher's exact test. Actuarial analysis was used to determine stability rates (alive without DP) at three month intervals. Stability rates were then compared between the Normal H V Group and the Long H V Unpaced Group and between Paced and Unpaced Long H V Groups.

Results

The clinical data of the three groups are summarized in Tables I and II The three groups of patients were similar in age sex NYHA classification general medical condition type of heart disease and the presence of bundle branch block or hemiblock on the peripheral ECG

The H V intervals were similar in the Long H V Paced and Unpaced Groups. These H V intervals were significantly longer than those of

[illegible]
† [illegible]

Table I Patient profile

	Normal HV	p <	Long HV unpaced	p <	Long HV paced	p <	Normal HV	p <	Both long HV groups
	18 pts		17 pt		18 pts		18 pts		35 pts
Age	68.2 ± 13†	NS	69.3 ± 11	NS	71.3 ± 8	NS	68.2 ± 13	NS	70.3 ± 9
Sex: M/F	10/8	NS	9/8	NS	14/4	NS	10/8	NS	23/12
NYHA Class	1.6 ± 7	NS	1.9 ± 7	NS	1 7 ± 7	NS	1.6 ± 7	NS	1.8 ± 7
Class 2° to Angina	1.4 ± .6	NS	1.6 ± .5	NS	1.3 ± .6	NS	1 4 ± .6	NS	1.5 ± .6
Class 2° t CHF	1.3 ± 7	NS	1 7 ± .8	NS	1.6 ± .8	NS	1.3 ± 7	(.10)	1.6 ± .7
General medical condition	1.8 ± 7	NS	2.1 ± 7	NS	1.7 ± .6	NS	1.8 ± 7	NS	1.9 ± 7
Primary Conduction dis.	9 pts	NS	4	NS		NS	9	NS	11
Coronary artery disease	6	NS	9	NS	6	NS	6	NS	15
Other heart disease	3	NS	4	NS	5	NS	3	NS	9
H-V interval (msec.)	44 1 ± 7	.001	67 4 ± 8	NS	71.9 ± 9	.001	44 1 ± 7	.001	69 7 ± 8
Months follow-up	22.3 ± 17	.001	63 ± 5	.001	2[illegible] ± 13	NS	22.3 ± 1	—	—
Continued symptoms during follow-up‡	9/18	NS	9/1	.04	[illegible]/18	(.11)	9/18	—	—

*pts = patients

†Numbers ± standard deviation.

‡Patients with nonsudden deaths excluded, those with sudden death (or progression to heart block in unpaced patients, all of whom had symptoms) [illegible] included

the Normal H V Group ($p < 0.001$) Cardiomegaly was insignificantly more common in the Long H V Groups. Congestive heart failure was similar between Long H V Groups, but significantly more common in the Long H V Paced than in the Normal H V Group. Cardiomegaly combined with either angina, congestive heart failure, or both occurred to a similar extent between Long H V Groups, and more frequently than in the Normal H V Group (Table II)

The fate of paced and unpaced patients as a function of H V interval is outlined in Fig 1

There were no deaths in the 18 unpaced patients who made up the Normal H V Group. This is in marked contrast ($p < .002$) to the eight of 17 patients in the Long H V (≥ 60 msec.) Unpaced Group who died. The eight deaths in the Long H V Unpaced Group also exceeded the three deaths in the Long H V Paced Group ($p < .06$) When these three of 18 patients who died in the Long H V Paced Group were compared to the 100 per cent survival among the 18 patients of the Normal H V Group, there was no statistical difference.

Of the nine survivors in the Long H V Unpaced Group, three had documented progression (DP) to complete heart block, with a wide QRS altered from previous conducted rhythm, and ventricular rates between 20 and 35 beats per minute. All had syncope or profound weakness. Six patients remained stable (alive without DP) In marked contrast, 15 patients in the Long H V Paced Group remained clinically stable although inhibition of their pacers during routine follow up revealed progression to heart block in four Thus the risks of death and the effects of advanced heart block were much greater ($p < .00$[illegible]) in the Long H V Unpaced Group

The risks for unpaced patients were even greater when an H V interval of 65 msec or longer was considered (Fig. 1).

Sudden death occurred in three [illegible] patients who died in the Long H V Un[illegible] Group. There were no sudden deaths in [illegible] the other two groups (Fig 1) Sudden [illegible] syncope at the time of progression to [illegible] occurred in six of 17 Long H V Unpa[illegible] but in none of 18 Long H V Pac[illegible] ($p < .03$)

Actuarial analysis (Fig. 2) highl[illegible] ity in the clinical courses of th[illegible] When nonsudden deaths were ex[illegible] evaluation of the effects of a [illegible] maker (Fig. 3), there was 100 per [illegible] the Normal H V and Long H[illegible] after 62 and 60 months, respe[illegible] H V Unpaced Group, there [illegible] after 18 months.

The mean follow-up per[illegible] Paced Group was 23 mont[illegible]

Table II The fate of paced and unpaced patients related to clinical features

	Normal H V group, 18 patients (all unpaced)				Long H V paced group 18 patients				Long H V unpaced group 17 patients			
Feature	Patients	Deaths non sudden	Deaths sudden	DP† to HB	Patients	Deaths non sudden	Deaths sudden	DP to HB	Patients	Deaths non sudden	Deaths sudden	DP to HB
(Overall)	18	0	0	0	18	3	0	4	1	5	3	3
Syncope	14	0	0	0	10	1	0	3	11			2
Dizziness	4	0	0	0	8		0	1	6	3	1	1
Angina to Class II/III/IV	5/1/0	0	0	0	4/1/0	2/0/0	0	0	9/0/0	1/0/0	2/0/0	1/0/0
CHF to Class II/III/IV	1/2/0	0	0	0	8/1/0‡	1/0/0	0	1/0/0	4/4/0	2/0/0	0/2/0	0
Cardiomegaly	5	0	0	0	10	1	0	2	10	4	3	2
Cardiomegaly & Angina/CHF/Both	0/0/1§	0	0	0	1/4/2	0	0	0/1/0	3/2/3	1/2/0	1/0/*	1/0/0
Primary conduction disease	9	0	0	0	7	0	0	2	4	1	1	1
Coronary artery disease	6	0	0	0	6	3	0	0	9	2		1
Other heart disease	3	0	0	0	5	0	0	2	4	2	0	1
Antiarrhythmic drugs	3	0	0	0	7	3	0	1	4	0		0
Digitalis	3	0	0	0	5	1	0	1	8	2		0
Normal QRS	2	0	0	0	1	0	0	0	4	1	0	0
Normal QRS & 1 AVB	0	0	0	0	2	0	0	0	2	1	0	0
RBBB	0	0	0	0	0	0	0	0	0	0	0	0
RBBB & 1 AVB	0	0	0	0	0	0	0	0	1	0	0	1
RBBB & hemiblock	8¶	0	0	0	3	1	0	0	1	1	0	0
RBBB & hemiblock & 1 AVB	1	0	0	0	4	1	0	1	1	0	1	0
LBBB	4	0	0	0	4	0	0	0	4	1	0	1
LBBB & 1 AVB	0	0	0	0	2	0	0	1	3	1	0	1
Hemiblock only	3	0	0	0	1	0	0	1	1	0	1	0
Hemiblock & 1 AVB	0	0	0	0	0	0	0	1	0	0	0	0
IVCD	0	0	0	0	1	1	0	0	0	0	0	0
24 Ambulatory ECG	11	0	0	0	9	1	0	4	1	4	2	1
3-4 days unit monitor††	7	0	0	0	13	3	0	1	14	5	3	3

*The number of patients from the first column in each group are compared for each feature See Fig. 1 for statistical comparison of deaths and DP

†DP to HB = documented progression to advanced heart block (For this table only the term "DP to HB" is also applied to paced patients). CHF = congestive heart failure AVB = atrioventricular block RBBB = right bundle branch block, LBBB = left bundle branch block; IVCD = diffuse intraventricular conduction defect

‡p < .04 vs Normal HV Group

§p < .02 vs. both long H V groups, considered separately or together

¶ p < .02 vs Long H V Unpaced Group

Minimum of 24 using Avionics system (Del Mar Avionics, Irvine CA 94304) In the last year most patients have had 2 to 3 days monitoring with Avionics or Cardiocassette (Cardiodyne, Inc Cupertino, Ca 95104) units

††In cardiac or intermediate cardiac care unit (ICCU) Most ICCU monitors are telemetry type (HP 78100, 78101A, Hewlett Packard, Waltham, MA 02154) allowing full ambulation and activity Many patients had both Avionics or Cardiocassette and unit monitoring

Long H V Unpaced Group was followed for a mean of 6 months This difference was significant. The short follow up in the Long H V Unpaced Group was due to early death or documented progression to a high degree of AV Block. Follow up of the Normal H V Group averaged 22 months.

During the follow up period symptoms continued in nine of 18 patients in the Normal H V Group (Table I) and (excluding patients with nonsudden death) in nine of 12 subjects in the Long H V Unpaced Group, and in two of 15 Long H V Paced patients. Of the four patients not included as part of the Normal H V Group because they received permanent pacers, syncope recurred in two In one of these a Holter monitor recorded normal sinus rhythm during syncope

A spectrum of intraventricular conduction defects occurred in each group (Table II) No individual bundle branch block pattern was

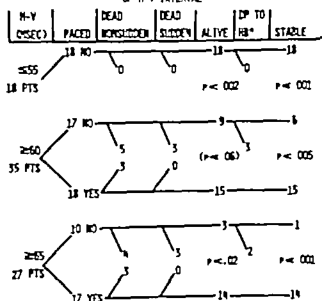


Fig. 1 The fate of paced and unpaced patients as function of H V interval. H V intervals are in msec. "Stable" means that neither death nor DP occurred. DP to HB as defined in *Materials and methods*-documented progression to advanced heart block requiring pacemaker implantation in previously unpaced patients. Four paced patients were found to be in heart block during pacer check-ups, but as they were asymptomatic, they were considered clinically stable.

significantly associated with increased risk of death or progression to heart block. One of four patients in the Long H V Unpaced group with left bundle branch block (LBBB) progressed to heart block. This is of interest in view of the suggestion[33] that H V intervals may be normally longer in the presence of left bundle branch block. None of the six patients in the Long H V Unpaced Group without bundle branch block or hemiblock had sudden death or DP. There were two nonsudden deaths in this group, however so that only four remained stable.

Discussion

There have been many reports dealing with the risk of progression to complete heart block in patients with bundle branch block on the peripheral ECG.[11-26] Recently attempts have been made using intracardiac recordings to segregate those patients with a high risk of progression of their conduction disturbance by evaluating the function of the remaining fascicle in bifascicular block (e.g., right bundle branch block and abnormal left axis deviation).[27-36]

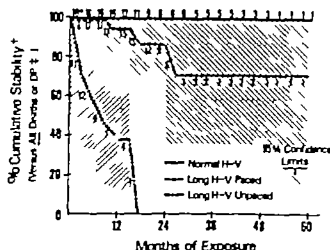


Fig. 2 Actuarial analysis based on samples at 3 month intervals, including death due to all causes. Number of patients entering each 3 month sampling period. Stability = alive without DP. DP = as defined in *Materials and methods*-documented progression to advanced heart block requiring pacemaker implantation in previously unpaced patients.

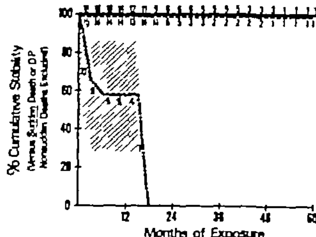


Fig. 3 Actuarial analysis based on samples at 3 month intervals, including only sudden death and DP. Conventions as for Fig. 2.

Previous studies have attempted to link the risk of developing syncope complete heart block, and sudden death to the presence of a prolonged H V interval. Some investigators have found prolonged H V intervals (recorded in normal sinus rhythm) in most patients who have chronic bifascicular block with documented intermittent heart block[*] and have, therefore, recommended permanent pacemakers in all patients with prolonged H V intervals and bifascicular block, even if the patients are asymptomatic. In contrast, others have recommended that no pace-

maker be implanted in patients without neurologic symptoms regardless of the presence of marked (≥ 80 msec.) H V prolongation Even in the presence of neurologic symptoms, the significance of a prolonged H V interval has not been clear in earlier studies. In one study involving a mixed group of patients with bifascicular block including those with and without symptoms or documented heart block, patients who received permanent pacemakers seemed to do better One group of investigators considered the problem of transient neurologic symptoms in 19 patients with bundle branch block. Complete AV block had been documented in seven of these and in six neurologic symptoms were observed in the absence of electrocardiographic evidence of AV block. In the remaining six patients the cause of symptoms was unclear but the H V interval was greater than 60 msec. in only three of these six patients. A recent study of 121 patients with chronic bundle branch block, including 0 with syncope or dizziness, found a high incidence of sudden death and progression to heart block especially with H V ≥ 70 and heart failure There were no control groups, however comparable to the Long H V Paced and Normal H V Groups of the present study It was not clear how many with sudden death or progression to heart block had had syncope or dizziness, and patients with other conduction or rhythm disorders were not stated to be excluded When patients with atrioventricular node disease are included progression to heart block is usually at the nodal level. In another series, 12 of 21 patients who died within one hour of onset of symptoms had a history of ventricular arrhythmias four of these deaths were medically attended and were due to ventricular fibrillation three of these four had a history of ventricular arrhythmias. The prognostic implications of a prolonged H V interval have therefore, remained in dispute largely due to the great number of variables among patient groups studied, and the absence of suitable control populations.

We have tried to reduce the number of variables in assessing the prognostic significance of the H V interval. All patients studied presented with the common clinical problem of symptoms consistent with intermittent heart block, but ECG monitoring and medical neurological evaluation failed to document heart block or other cause for symptoms. Adequate controls were attained by comparing the clinical courses of patients with normal H V intervals who remained unpaced and two groups of medically similar patients with prolonged H V intervals, half of whom received permanent pacers.

Among the Long H V Groups in this series, three unpaced and four paced patients subsequently developed advanced heart block. However a direct comparison of the incidence of progression to advanced heart block in paced and unpaced groups is difficult and may not be valid. Among the unpaced, progression to heart block would be expected to cause symptoms, eventually resulting in either death or documentation of the heart block. Once paced intermittent heart block will be asymptomatic and would be documented only if heart block by chance existed during brief periods of pacer inhibition at follow up visits. Further it has been shown that following implantation of a pacemaker previously established heart block may progress further improve, or remain stable Thus, lack of progression to heart block in paced patients does not suggest that the pacer was unnecessary

Continued symptoms during the follow-up period were common in both unpaced groups. Among those with long H V intervals, these symptoms were frequently associated with early sudden death or documented progression to heart block, while neither occurred among patients with normal H V intervals. We do not know whether the sudden deaths were due to ventricular tachyarrhythmias or heart block. Patients with histories of ventricular tachyarrhythmias had been excluded from this study and again, sudden death did not occur in any of the Long H V Paced patients. Prolonged ambulatory ECG monitoring, even for weeks until symptoms occur during monitoring, may be helpful in some patients,[11] but because of the early risks in symptomatic patients with prolonged H V intervals, we believe such patients should receive an implantable pacer with prolonged monitoring reserved for patients with normal H V intervals.

Conclusions

1 Patients in this study with intermittent neurologic symptoms which remained unexplained after full medical neurologic evaluation, including ECG monitoring were at high risk of early sudden death or progression to heart block if their H V interval was 60 msec. or more. These

risks were further magnified if the HV interval was greater than 65 msec

2. The early mortality or risks from progression to heart block were eliminated in patients with HV ≥ 60 msec by implantation of a permanent pacemaker even though intermittent heart block could not be documented before implant

3. Bundle branch block or hemiblock was absent in nine of our 35 patients with prolonged HV interval. Since none of the six unpaced patients in this subgroup had sudden death or progression to heart block their risks remain to be fully assessed

4. Patients with prolonged HV intervals had a trend toward higher mortality rate even when paced than patients with normal HV interval in spite of similarities in age NYHA class and general medical classification

5. Bundle of His studies can assist in predicting the clinical course of patients such as those described in this study

Summary

Paced and unpaced control groups were followed to establish the roles of pacers and infranodal (HV) conduction in 59 patients with symptoms consistent with intermittent heart block (HB) To reduce the number of variables compared with previous studies, patients were included only when (1) prior ECG monitoring and medical neurologic evaluation failed to document HB or other cause for symptoms (2) His bundle studies were normal or showed only HV prolongation, and (3) there was no history of a recent myocardial infarction. Of 35 patients with prolonged HV interval, 18 received permanent pacers, while 17 remained unpaced. Eighteen unpaced patients constituted the normal HV Group (after two were lost to follow up and four received pacers) All groups were similar in types of heart diseases, NYHA classification general medical condition age and sex, thus providing adequate controls.

All patients with normal HV intervals remained stable (no deaths or progression to HB) for a mean follow-up period of 22 months. Among 18 patients with prolonged HV intervals who received pacers, there were three deaths, none sudden, during a mean of 23 months four patients developed HB unaccompanied by symptoms. Among 17 patients with prolonged HV intervals who were not paced, eight died (three suddenly) and three progressed to HB with symptoms, leaving only six stable after six months follow up All these parameters were significantly worse in the unpaced patients with prolonged HV intervals.

These results suggest that patients with intermittent symptoms consistent with heart block whose HV interval is ≥ 60 msec, should receive a permanent pacer even if intermittent HB cannot be documented before implant.

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risks were further magnified if the H V interval was greater than 65 msec

2. The early mortality or risks from progression to heart block were eliminated in patients with HV ≥ 60 msec by implantation of a permanent pacemaker even though intermittent heart block could not be documented before implant.

3. Bundle branch block or hemiblock was absent in nine of our 35 patients with prolonged H V interval. Since none of the six unpaced patients in this subgroup had sudden death or progression to heart block, their risks remain to be fully assessed

4. Patients with prolonged H V intervals had a trend toward higher mortality rate even when paced, than patients with normal H V intervals, in spite of similarities in age NYHA class, and general medical classification

5. Bundle of His studies can assist in predicting the clinical course of patients such as those described in this study

Summary

Paced and unpaced control groups were followed to establish the roles of pacers and infranodal (H V) conduction in 53 patients with symptoms consistent with intermittent heart block (HB) To reduce the number of variables compared with previous studies, patients were included only when (1) prior ECG monitoring and medical neurologic evaluation failed to document HB or other cause for symptoms ( ) His bundle studies were normal or showed only H V prolongation, and (3) there was no history of a recent myocardial infarction Of 35 patients with prolonged H V interval, 18 received permanent pacers, while 17 remained unpaced. Eighteen unpaced patients constituted the normal H V Group (after two were lost to follow-up and four received pacers) All groups were similar in types of heart diseases, NYHA classification general medical condition, age and sex, thus providing adequate controls.

All patients with normal H V intervals remained stable (no deaths or progression to HB) for a mean follow up period of 22 months. Among 18 patients with prolonged H V intervals who received pacers, there were three deaths, none sudden, during a mean of 23 months four patients developed HB unaccompanied by symptoms. Among 17 patients with prolonged H V intervals who were not paced eight died (three suddenly) and three progressed to HB with symptoms, leaving only six stable after six months follow up. All these parameters were significantly worse in the unpaced patients with prolonged H V intervals.

These results suggest that patients with intermittent symptoms consistent with heart block, whose H V interval is ≥ 60 msec, should receive a permanent pacer even if intermittent HB cannot be documented before implant

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bnormal interventricular septal motion ollowing cardiac surgery Clinical surgical chocardiographic and radionuclide correlates

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he use of echocardiography has permitted oninvasive analysis of interventricular septal inction. Prior studies have shown abnormal ·ptal motion in 42 to 91 per cent of patients llowing cardiac surgery for a variety of congen l and acquired heart diseases.[1-] However it is ›t understood why some patients develop abnor al motion and others do not. In this prospective udy (1) we examined the clinical, hemody mic, surgical, and echocardiographic data of a up of patients about to undergo cardiac rgery (2) we attempted to identify those itures, if any which distinguished patients who l from those who did not develop abnormal tal motion and (3) we used gated cardiac od pool scintigraphy to further define the ent of the septal abnormality

thods

orty five patients (mean age 51 years, range to 69 years) scheduled to undergo cardiac gery at the Massachusetts General Hospital a variety of congenital and acquired cardiac ases were selected for this prospective study Each underwent an echocardiographic examination one day preoperatively and again 8.7 ± 0.3 days postoperatively Only those patients with technically adequate studies were included All had normal septal motion before surgery Patients developing left bundle branch block or requiring ventricular pacing postoperatively were excluded.

The echocardiograms were obtained using a 2.25 mHz Aerotech 10 cm. focused transducer and a Smith Kline Instruments 20A ultrasonoscope interfaced to a Honeywell 1856 strip chart recorder The patients were examined in the supine position with the transducer held perpendicularly to the chest wall in the third or fourth intercostal space. The damping and gain control settings were adjusted for optimal demonstration of the right and left endocardial surfaces of the interventricular septum and the endocardial and epicardial surfaces of the left ventricular posterior wall at a level just below the mitral leaflet echoes (Fig. 1) The right ventricular end-diastolic dimension (RVIDd) was measured at the peak of the R wave of the simultaneously recorded electrocardiogram as the vertical distance between the endocardial echo of the anterior right ventricular wall and the endocardial echo from the right side of the interventricular septum The left ventricular end-diastolic dimension (LVIDd) was measured from the endocardial echo of the left side of the interventricular septum to the endo-

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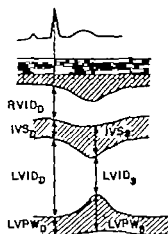


Fig. 1 Echocardiogram schematic through right and left ventricle illustrating how measurements were made. $RVID_D$ = right ventricular diastolic dimension, IVS_D = diastolic thickness of the interventricular septum, IVS_S = systolic thickness of the interventricular septum, $LVID_D$ = left ventricular diastolic dimension, $LVID_S$ = left ventricular systolic dimension, $LVPW$ = diastolic thickness of the left ventricular posterior wall, $LVPW$ = systolic thickness of the left ventricular posterior wall.

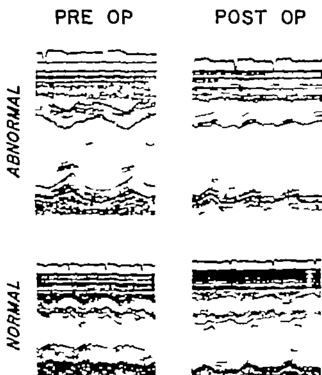


Fig. 2. Examples of pre- and postoperative echocardiograms performed on two of the study patients undergoing mitral valve replacement. *The patient illustrated in the upper panels* developed abnormal septal motion postoperatively while *the patient in the lower panel* remained normal.

cardial echo from the posterior left ventricular wall. The left ventricular end-systolic dimension (LVIDs) was measured at the time of maximal anterior motion of the left ventricular posterior wall and was taken as the vertical distance ... en the left septal endocardial echo and the ... dial echo from the left ventricular poste... wall. The right and left ventricular chamber ... thus measured were corrected for body surface area. The thickness of the interventricular septum and left ventricular posterior wall were measured at end diastole and end systole. The per cent systolic thickening of both these structures was taken as the end systolic thickness minus the end-diastolic thickness divided by the end-diastolic thickness multiplied by 100. Septal motion was also graded in a qualitative fashion. Posterior systolic motion of the left side of the septum greater than 2 mm. was considered normal. Absent systolic motion or paradoxic anterior systolic motion was considered abnormal. All measurements were made independently by two observers. When differences arose they were settled by consensus. The presence of a pericardial effusion was determined using the method of Horowitz and associates.

Nine of the 45 study patients underwent gated cardiac blood pool scanning one day prior to and again 9.2 ± 0.4 days following cardiac surgery. Gated scans were performed with a Searle HP Pho Gamma III Anger camera positioned over the patient to obtain multiple left anterior oblique images of the heart. Twenty mCi of Technetium 99m electrolytically bound to human serum albumin were injected via an antecubital vein. Several minutes were allowed for equilibration within the blood pool. An ECG synchronizer* allowed the simultaneous acquisition of end-diastolic and end-systolic images and each was collected for approximately one tenth of a cardiac cycle. Approximately 400 000 counts were accumulated for each end-diastolic and end systolic image pair and were stored in the memory of a PDP 9 computer.† Imaging time was about 7 minutes for each projection. Images were displayed on a cathode ray tube. The left anterior oblique image pair which best delineated the septum was selected for analysis. The systolic motion of the entire septum from apex to base was assessed qualitatively by rapid alternation

*Brattle Instruments, Cambridge, Mass.
†Digital Equipment Company

Table I Preoperative catheterization data of the 40 patients undergoing cardiopulmonary bypass

	Postoperative septal motion		
	Abnormal (31)	*Normal (9)*	*P value*
PCW (mm. Hg)	20 ± 2 (n = 24)	20 ± 3 (= 9)	NS
LVEDP (mm. Hg)	19 ± 2 (n = 22)	18 ± 2 (n = 8)	NS
systolic (mm. Hg)	146 ± 8 (n = 16)	131 ± 10 (n = 8)	NS
(mm. Hg)	6 ± 1 (n = 23)	6 ± 1 (n = 9)	NS
EDP (mm. Hg)	7 ± 1 (= 23)	7 ± 2 (n = 8)	NS
systolic (mm. Hg)	57 ± 7 (= 19)	48 ± 7 (n = 8)	NS
A mean (mm. Hg)	30 ± 2 (= 23)	30 ± 5 (n = 9)	NS
ARI (units)	4.1 ± 1 (= 24)	4.3 ± 2 (n = 7)	NS
index (liters/min. /M²)	2.9 ± 0.2 (= 24)	2.9 ± 0.3 (= 7)	NS
ection tion (%)	53 ± 3 (n = 19)	58 ± 7 (n = 5)	NS

Table II Operative procedures and clinical diagnoses of the 40 patients undergoing cardiopulmonary bypass

	Postoperative septal motion			
	Abnormal (31)		*Normal (9)*	
Aortic valve replacement	12		2	
AS		1		0
AR		8		0
AS/AR		2		2
Aortic dissection		1		0
Mitral valve replacement	8		6	
MR		2		3
MS		3		2
MS/MR		3		1
Open mitral commissurotomy	1		0	
Aortic and mitral valve replacement	3		0	
AR & MR		3		0
Coronary artery bypass graft	6		1	
LAD		4		1
no LAD		2		0
Pulmonic valvuloplasty	1		0	

the end-diastolic and end-systolic image Motion of the superior basal and inferior septum was judged by two independent ers who did not know whether the scans performed pre- or postoperatively Move- of the septum toward the posterior left ntricular wall was considered normal. Absent motion or paradoxic motion away from the ventricular posterior wall were considered ormal. Polaroid photographs of the oscilli- e images were then taken as hard copy Again t knowing which image was pre- or postop- , qualitative estimates of the extent of thickening were made for each patient of the other data.

e preoperative cardiac catheterization data were reviewed without knowledge noninvasive study findings. Right and left rt pressures, Fick cardiac outputs and the of supravalvular aortic, selective coronary left ventricular angiography were recorded. operative technique used in each of the 45 patients was reviewed, again independently other data. The following information was the nature of the operation performed approach (median sternotomy left acotomy) the techniques used for intraoperative myocardial preservation cardiopulmonary bypass time and aortic cross-clamp time whether the pericardium was closed postoperatively and whether the pleural spaces were entered, the left ventricular drain site (left ventricular apex, pulmonary vein) the presence or absence of an uncorrected left or right ventricular volume over load state. Any patient developing clincial, electrocardiographic, or serum enzyme evidence of an intra or postoperative myocardial infarction was excluded.

Statistical analyses were performed using Student's t test for unpaired data and Chi-squared analysis.

Results

The study group consisted of 45 patients. Five patients underwent cardiac surgical procedures not requiring cardiopulmonary bypass. All had normal postoperative septal motion. This group consisted of two patients with a "closed" mitral commissurotomy through a median sternotomy one with a patent ductus arteriosus ligation one with an aortic coarctation repair and one with a descending thoracic aneurysm resection. Forty patients underwent cardiac surgical procedures employing cardiopulmonary bypass. Of these

Table III Intraoperative data of the 40 patients undergoing cardiopulmonary bypass

	Postoperative septal motion	
	Abnormal (31)	*Normal (9)*
Incision		
Median sternotomy	31	9
Perfusion site		
Aortic arch	30	9
Femoral artery	1	0
Venous return		
Right atrium	30	9
Femoral vein	1	0
K arrest	18	1
Bypass time (minutes)	87 ± 6	72 ± 8
Aortic cross clamp time (minutes)	47 ± 5	30 ± 4
Pericardium closed	7	4
Pleural space entered	13	2
Residual LV volume overload	6	3
Residual RV volume overload	3	0

Table IV Echocardiographic data of the 40 patients undergoing cardiopulmonary bypass

	Abnormal postoperative septal motion (31)		*Normal postoperative septal motion (9)*	
	pre op	*post op*	*pre op*	*post op*
RVIDd (mm.)	8 ± 1	12 ± 1	8 ± 1	8 ± 1
LVIDd (mm.)	34 ± 1	28 ± 1	32 ± 2	31 ± 1
RV/LV	0.34 ± 0.01	0.45 ± 0.04	0.26 ± 0.02	0.26 ± 0.02
LVIDs (mm.)	23 ± 2	22 ± 1	20 ± 1	21 ± 1
IVSd (mm.)	10 ± 1	10 ± 1	10 ± 1	10 ± 1
% septal systolic thickening	42 ± 4	22 ± 4	47 ± 7	48 ± 6
LVPWd (mm.)	10 ± 1	10 ± 1	10 ± 1	10 ± 1
% LVPW systolic thickening	63 ± 6	64 ± 5	73 ± 7	62 ± 7
Pericardial effusion	0	2	0	1

31 had abnormal and nine had normal postoperative septal motion (Fig. 2). Thus there was a significant association between the development of abnormal postoperative septal motion and the use of cardiopulmonary bypass ($p < 0.001$).

Among the 40 patients undergoing cardiopulmonary bypass, the 31 patients with abnormal postoperative septal motion were compared with the nine patients whose septal motion remained normal after surgery. Preoperative catheterization data comparing these two groups is shown in Table I. There was no difference between the two groups in preoperative right and left heart pressures, cardiac index, and left ventricular ejection fractions.

The clinical diagnoses and surgical procedures are listed in Table II. Twelve of 14 patients undergoing isolated aortic valve replacement developed abnormal septal motion while eight of 14 patients undergoing isolated mitral valve replacement developed abnormal septal motion. The difference was not significant. Although the number of patients studied with coronary artery disease was small, the presence or absence of a critical left anterior descending coronary artery stenosis did not seem to influence the type of postoperative septal motion observed.

Review of the intraoperative surgical data (Table III) revealed that there were no significant differences between the two groups in the surgical approach, the surgeons performing the operation, the cannulation technique for cardiopulmonary bypass, the time of total cardiopulmonary bypass, the time the aorta was cross-clamped, and the left ventricular drain site. Entry into the left or right pleural spaces and closure of the pericardium following the procedure were also similar for the groups. There were no significant differences between the two groups in the incidence of residual right or left ventricular volume overload due either to uncorrected valvular regurgitation or paraprosthetic leaks. Three of the nine patients with normal septal motion following cardiopulmonary bypass had residual postoperative left ventricular volume overload. Two of the three underwent mitral valve replacement and had hemodynamically insignificant aortic regurgitation left uncorrected. The third patient developed significant aortic regurgitation secondary to a paraprosthetic leak immediately following aortic value replacement. The remaining six patients with normal postoperative septal motion had no evidence of residual uncorrected left ventricular volume overload. In addition, six of the 31 patients with abnormal postoperative septal motion had uncorrected left ventricular volume overload which was judged insignificant at the time of cardiac catheterization and surgery (three patients undergoing mitral valve replacement with trivial aortic regurgitation and three

patients undergoing aortic valve replacement with trivial mitral regurgitation).

Potassium cardioplegic arrest solution was used more commonly during cardiopulmonary bypass in those patients developing postoperative abnormal septal motion (18 of 31 vs 1 of 9 $p < 0.02$). The surgical procedures on all patients in both groups were performed under moderate hypothermia (28° C.) and topical cooling was done with iced Ringer's lactate solution. Coronary perfusion was not performed on any patient in either group.

The pre- and postoperative echocardiographic data are summarized in Table IV A postoperative pericardial effusion was present in one of the nine patients with normal and two of the 31 patients with abnormal septal motion.

Preoperatively echocardiographic RVIDd, LVIDd, and RVIDd/LVIDd were similar in both groups of patients. Postoperatively however the patients with abnormal motion developed a significant increase in their RVIDd (8 ± 1 to 12 ± 1 m.m, $p < 0.001$) while those with normal motion remained unchanged (8 ± 1 to 8 ± 1 m.m, P = NS). The postoperative LVIDd decreased significantly in those with abnormal motion (34 ± 1 to 28 ± 1 m.m, $p < 0.001$) but remained unchanged in those with normal motion (32 ± 2 vs 31 ± 1 m.m, P = NS). A significant increase in the RV/LV ratio was noted in the group with abnormal motion (0.24 ± 0.02 to 0.48 ± 0.04, $p < 0.001$). This ratio remained unchanged in those with normal motion (0.26 ± 0.02 vs 0.28 ± 0.02, P = NS)

Preoperatively the septal and left ventricular wall thickness in diastole as well as the per cent systolic thickening of both these structures were similar in both groups. However postoperatively there was a significant reduction in the per cent systolic thickening of the septum in the group with abnormal motion (42 ± 4 to 23 ± 4 per cent, $p < 0.001$) while those with normal motion remained unchanged (47 ± 7 vs 48 ± 5 per cent, P = NS). There was no significant postoperative change in the per cent systolic thickening of the left ventricular posterior wall in either group.

Pre- and postoperative gated cardiac blood pool scans were obtained on nine of the study patients, all of whom had abnormal postoperative septal motion echocardiographically The postoperative scans on all nine patients demonstrated decreased systolic septal thickening when compared to the preoperative study In addition, absent or frankly paradoxic systolic motion was noted. In each instance, the motion abnormality of the upper basal septum was more marked than the lower apical septum (Fig. 3)

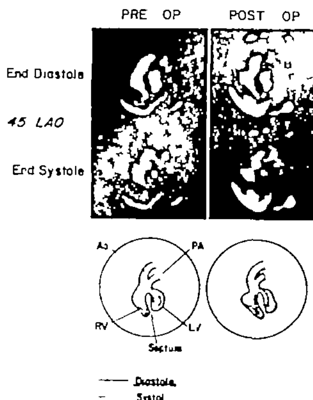


Fig. 3. Pre- and postoperative 45 degree left anterior oblique end-diastolic and end-systolic gated cardiac blood pool scans on one of the study patients undergoing aortic valve replacement. The accompanying schematic diagrams illustrate the abnormal septal motion in the postoperative study

Discussion

Although the development of abnormal echocardiographic interventricular septal motion following cardiac surgery has been previously described,[3-6] the mechanism and significance of this finding has remained obscure. In the present study the clinical, hemodynamic, angiographic, echocardiographic, and gated cardiac blood pool scan data of a group of patients undergoing cardiac surgery were studied prospectively in an attempt to define the factors associated with development. The results of this study and of others[7] indicate that the development of abnormal septal motion and *systolic thickening* is not a nonspecific result of thoracotomy and that the use of cardiopulmonary bypass is a necessary

prerequisite for its development. The data also indicate that postoperative paradoxical septal motion is not related to the preoperative hemodynamics. With the possible exception of the use of potassium arrest solution, differences in surgical technique cannot be invoked as playing a significant role in the development of this septal motion abnormality.

In 1973 Miller and colleagues[4] called attention to the fact that patients frequently developed abnormal septal motion following mitral valve replacement. In addition they noted that the development of a paraprosthetic leak with resultant severe mitral regurgitation was often associated with normalization of the septal motion. Similar observations have been made following aortic valve replacement. In the present study the presence or absence of uncorrected right or left ventricular volume overload was not a major determinant in the development of normal or abnormal postoperative septal motion in the majority of the study patients. Although the development of a paraprosthetic leak with severe valvular regurgitation appears to be associated with normal postoperative septal motion the [present] study demonstrates that presence of [normal] septal motion postoperatively cannot be [tak]en as evidence of a significant paraprosthetic leak or uncorrected left ventricular volume overload.

Large pericardial effusions may alter apparent septal motion as an artifact of unrestrained whole heart motion. In the present study a postoperative pericardial effusion was present in one of the nine patients with normal and in two of the 31 patients with abnormal septal motion. Thus it is unlikely that pericardial effusion plays a major role in the development of abnormal septal motion in the majority of postoperative patients.

Recently Payvandi and co-workers[6] reported apparent right ventricular enlargement and paradoxic septal motion in five patients with congenital complete absence of the pericardium. In addition they observed similar findings in 14 of 16 patients who underwent complete pericardial stripping without cardiopulmonary bypass. They postulated that the absence of the pericardium may result in altered cardiac position within the thorax and exaggerated whole heart motion. Absence of the pericardium may result in apparent right ventricular enlargement while exaggerated whole heart motion may lead to paradoxic septal motion. They went on to speculate that the paradoxic septal motion frequently seen following cardiac surgery might result from the common surgical practice of leaving the anterior pericardial sac open. While the apparent right ventricular enlargement noted postoperatively in the present study could have resulted from an altered cardiac position within the thorax, the septal motion abnormality would be more difficult to explain. In the present study there was no significant difference in the occurrence of abnormal septal motion in patients with or without closure of the pericardium. This observation plus the inability of the "open pericardium hypothesis" to explain the diminution in the extent of septal thickening in those patients with abnormal postoperative motion makes it unlikely that the integrity of the pericardium is an important determinant of this postoperative phenomenon.

Burggraf and Craige[3] first suggested that the septal motion abnormality seen following cardiac surgery may result from clinically inapparent septal ischemia during cardiopulmonary bypass. This explanation is indirectly supported by the present study. A significant reduction in septal systolic thickening was demonstrated postoperatively in those patients with abnormal motion while no change in septal thickening was demonstrated in those with normal motion. A similar echocardiographic observation has recently been made by Righetti and associates in 22 patients following coronary artery bypass grafting. Kerber and co-workers[19] have demonstrated in the open chest dog that graded septal ischemia, as measured by radioactive microspheres, impaired the ability of the septum to thicken during systole. Ross and Franklin have made similar observations. In addition, Corya and colleagues[11] have demonstrated abnormal changes in systolic wall thickening in patients with coronary artery disease with chronic ischemia.

If it can be concluded that the reduction in systolic septal thickening following cardiopulmonary bypass may be a manifestation of intraoperative septal ischemia, why do some patients develop this postoperative abnormality while others do not? It appears unlikely from the present study that significant disease of the left anterior descending coronary artery is an important factor in the development of septal paradox. Burggraf and Craige[3] suggested that the duration

of aortic cross-clamping during cardiopulmonary bypass may be an important determinant in the development of clinically inapparent myocardial (septal) ischemia with resultant paradoxic septal motion. The data from the present study demonstrate that cardiopulmonary bypass and aortic cross-clamp times were longer in those patients developing abnormal septal motion but that these differences did not reach statistical significance. However if this abnormality represented a global ischemic insult related to absent myocardial perfusion during cross-clamping, one might also expect similar ischemic changes reflected in LV posterior wall systolic thickening. Such changes were not observed in the present study

In light of the above the greater incidence of postoperative septal contraction abnormalities in those patients receiving potassium arrest cardioplegia in addition to systemic and topical hypothermia is difficult to understand. Potassium citrate arrest has been demonstrated to further reduce the myocardial oxygen requirements of the bypassed, vented heart.

In conclusion, reduced contraction and abnormal motion of the interventricular septum occur commonly but not invariably after cardiac surgery requiring cardiopulmonary bypass. The development of these motion abnormalities appear to be unrelated to the preoperative clinical diagnosis and hemodynamics. With the possible exception of the use of potassium cardioplegia, differences in surgical technique could not be identified which distinguished those with normal from those with abnormal postoperative septal motion. In addition, the presence or absence of postoperative pericardial effusion or uncorrected ventricular volume overload do not appear to be playing an important role in the majority of patients. Reduced systolic septal thickening with normal posterior wall thickening in the group with abnormal motion lends indirect support to the concept of selective intraoperative septal ischemia first proposed by Burggraf and Craige. Further work is necessary to determine the mechanism and clinical significance of this selective septal insult.

Summary

Interventricular septal motion was studied prospectively by echocardiography in 45 patients examined before and after cardiac surgery. In addition, nine of the patients underwent pre- and postoperative gated cardiac blood pool scintigraphy. All had normal septal motion preoperatively. Of the 40 patients whose surgery included cardiopulmonary bypass, 31 had abnormal and 9 had normal postoperative septal motion. All five patients without cardiopulmonary bypass had normal postoperative septal motion ($p < 0.001$). Among those patients undergoing cardiopulmonary bypass, there was no difference between those with normal and those with abnormal postoperative septal motion in clinical diagnosis, operative procedure, or surgical techniques (bypass time, aortic cross-clamp time, pericardium closed, prosthesis used) except that potassium arrest had been used more frequently in those with abnormal motion (18 of 31 vs 1 of 9, $p < .02$). Preoperatively there was no difference in echocardiographic right ventricular dimension (8 ± 1 vs 8 ± 1 mm., mean $\pm$ SEM). However postoperatively those with abnormal motion had a larger right ventricle than those with normal motion (12 ± 1 vs 8 ± 1 mm., $p < .005$). The postoperative percent systolic septal thickening decreased in those with abnormal motion (42 ± 4 per cent to 23 ± 4 per cent) ($p < 0.001$) and did not change in those with normal postoperative motion (47 ± 7 per cent to 48 ± 4 per cent). These findings were corroborated on gated cardiac blood pool scanning, and in addition demonstrated that when present, the motion abnormality was more marked at the upper than the lower septum. These findings confirm that postoperative abnormal systolic septal motion and thickening are common but not invariable following cardiopulmonary bypass and that they appear unrelated to preoperative clinical diagnosis, hemodynamics, or surgical technique.

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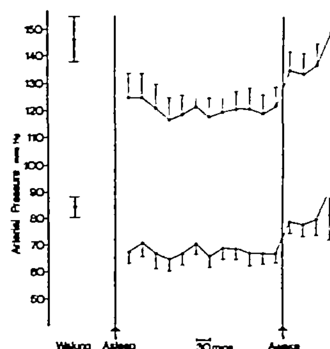


Fig. 1 The group data for the 18 untreated patients. The point at which the patient woke was determined and blood pressure was then averaged backwards throughout sleep over 30 minute periods, and forward for the first 2 hours after waking. In addition, the whole of the waking period prior to sleep was also determined. Figures indicate mean ± one standard error of the mean. It can be seen that there is no appreciable rise in pressure during sleep, but that once the patient is awake blood pressure begins to rise rapidly

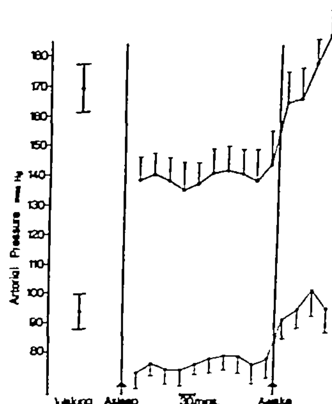


Fig. 2. The group data for the nine subjects who were currently receiving hypotensive drugs. The figure has been constructed in exactly the same fashion as for *Fig. 1*

average age 50 years (21 to 64) whose average casual blood pressure was 181/112 ± 8/4 mm. Hg SEM (range 144/104 to 220/125 mm. Hg) All had a casual diastolic pressure of greater than 100 mm. Hg. The hypotensive therapy included beta adrenergic receptor blocking drugs, sympathetic blocking drugs, and diuretics.

Results

The point in time at which the individual indicated that he or she had awakened from sleep was found and was taken as the reference point. Systolic and diastolic blood pressures were then averaged over 30 minute intervals, backwards through the whole of sleep and also forwards from this reference point for the first two hours after wakening. In addition, the average systolic and diastolic blood pressures for the whole of the waking period prior to sleep was also determined. In the untreated group the average length of sleep for the majority was 6½ hours, for the treated group it was less, some 5 hours.

The group data is illustrated in Figs. 1 and 2. In both groups it can be seen that systolic and diastolic blood pressure only show an appreciable rise (Group 1 13/11 mm. Hg; Group 2. 19/14 mm. Hg) *after* the subjects had awakened from sleep and a further rise (Group 1 14/12 mm. Hg; Group 2: 23/3 mm. Hg) occurred during the first two hours after awakening, during which time all had got out of bed and had been involved in washing, dressing, breakfasting and, in many cases, coming to hospital. The data do not show any appreciable rise in pressure before awakening and would seem to confirm that sleep and physical activity have a predominant influence on arterial pressure recordings during this time.

Discussion

Data concerning the nocturnal behavior of blood pressure are incomplete without a simultaneous electroencephalogram and we cannot, therefore, comment on the depth of sleep of any of these 27 people. Nevertheless, we were able to determine with considerable accuracy when each individual awoke from a prolonged period of sleep. In both untreated and treated subjects, an

appreciable rise in both systolic and diastolic pressure only occurred after wakening and there was a further increase once the person was out of bed. Thus, we were unable to confirm the findings of Millar Craig and colleagues that blood pressure rose significantly in the early morning and was independent of activity. Clearly we have analyzed our data independently of the actual time of day and related it to when the subject woke from sleep and later when he became involved in physical activity. We believe that if time is to be taken into account it has to be clearly related to such events, in order to avoid the introduction of artefacts.

Snyder and colleagues in 1964 first correlated the electroencephalogram with respiration, heart rate, and systolic blood pressure measured at five minute intervals with a sphygmomanometer in 12 healthy subjects during two or three nights of uninterrupted sleep. They described a fall in blood pressure averaging 20 per cent to a minimum about 2 hours after the beginning of sleep with gradual rise during the rest of the night to a level comparable to that of sleep onset." Richardson and colleagues[8] also correlated the electroencephalogram with blood pressure and heart rate and noted that waking, even for brief periods, always resulted in elevation of blood pressure and heart rate which coincided with recurrence of alpha rhythm and averaged 13/11 mm. Hg and 5 beats a minute. Smyth and colleagues[9] further demonstrated that no nocturnal rhythm of blood pressure was independent of sleep. As long ago as 1912 Brooks and Carroll noted that frequent interruption of sleep prevented the fall in pressure, and further pointed out that subjects who habitually slept by day and worked at night had lowest blood pressure during daytime sleep. Bevan and colleagues also failed to demonstrate any pattern of blood pressure behavior independent of sleep in their study of patients in whom blood pressure was continuously recorded in both a hospital and home environment.

The present study corroborates previous findings that the arterial blood pressure is dependent on activities such as sleep and physical exertion and indicates that one should be cautious in relating blood pressure levels specifically to time. In our experience, once the subject is awake and involved in physical activities, the blood pressure rises appreciably from that recorded during sleep. Such evidence is against the presence of an independent blood pressure rhythm related to time alone.

Summary

Twenty seven healthy people with a wide range of casual blood pressure readings (120/70 to 230/120 mm. Hg) had their blood pressure recorded continuously over a 24-hour period. Arterial pressure fell during sleep and only rose appreciably after the patients had awakened and a further rise was associated with physical activity once they were out of bed. This pattern was observed in 18 untreated patients and in nine currently receiving hypotensive treatment. This study suggests that arterial pressure is not specifically related to time and is chiefly governed by physical activity and sleep.

The basic data for this work was gathered while the author worked in the University Department of Cardiovascular Medicine and the Department of the Regius Professor of Medicine in Oxford. I am grateful to Professor Peter Sleight, Dr A. J. Honour, Dr L. J. Beilin, and Mr R. D. Carter for their help.

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Effect of Chagas' disease on arterial blood pressure

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American trypanosomiasis was first described in Brazil in 1909 Since that year various publications have been reported describing different clinical manifestations of the disease, but there is scant information in relation to arterial blood pressure and Chagas' disease.[1-4] It is known that Chagas' disease usually presents a fall in arterial blood pressure, but to the best of our knowledge this subject has never been adequately studied The accepted explanation for this hypotension has been a fall in cardiac output and a reduction the contractile force of the heart secondary to cardiomyopathy Anselmi and Moleiro in 1971 summarized what was known up to that date, confirming that a reduction in heart contractility occurs and suggested that this is the cause of the arterial hypotension

The purpose of this study was to compare the arterial blood pressure of chagasic patients with that of the general population of the same geographic area,[5] and also to investigate why and under which circumstances Chagas' disease lowers the arterial blood pressure

Materials and methods

One hundred and fifteen chagasic patients have been studied with a male/female ratio of 1 to 1 and a mean age of 39 ± 13 years. The diagnoses of the disease were based upon the epidemiology and the complement fixation serologic test (Machado-Guerreiro). All patients with doubtful positive reactions were excluded. In three cases the disease was believed to have been acquired by transfusions of infected blood. Most of these patients are affiliated to a health security plan and have a follow up from 10 to 20 years. All patients had a complete medical record, ECG and a chest x ray With all this information the following groups were established

A-1 Infected without heart failure In this group were included 86 patients. They had no evidence of clinical heart failure and the heart size was normal by x ray examination. Most of these patients had a normal ECG

A-2. Infected with heart failure This group included 29 patients with clinical evidence of heart failure and of cardiomegaly (cardiothoracic index greater than 0.50)

Another classification based upon body weight and height was.

B 1 Average ± 10 per cent higher than the ideal weight.

B 2. Ten per cent overweight From +10 per cent to +25 per cent higher than the ideal weight.

B-3 Obese More than 25 per cent higher than the ideal weight.

All data were compared with that obtained in an epidemiologic study of hypertension undertaken in Córdoba, Argentina.[5] In both studies the arterial blood pressure was taken in 95 per cent of the cases by the same author following the rules and methods given by Hamilton and colleagues and the World Health Organization Two readings were taken with an interval of 10 minutes and the average was used for

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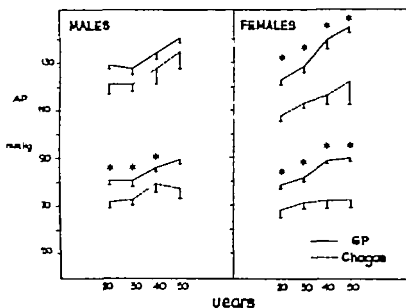


Fig. 1 Mean systolic and diastolic pressures for females and males for each ten year age group in the general population and in all Chagasic patients. *Solid line* = general population sample. *Broken line* = all Chagasic patients. ± P < 0.05 *Vertical bars* represent one SE.

statistical purposes. The arterial blood pressure was taken in the sitting position and the first and fourth phase of Korotkoff were used for the systolic and diastolic readings, respectively.

Blood pressure readings were made to the nearest of 5 mm. to 5 mm. Hg. No attempt was made to correct the reading in accordance with arm circumference. Student's t test was used in the statistical evaluation of the data.

Results

Chagasic population versus the general population. When these groups were compared by age and sex (Fig. 1), it may be seen that in all cases the mean arterial pressures of the chagasic population were lower than those corresponding to the general population. These differences were greater in the diastolic than in the systolic pressures and were greater in females than in males.

Chagasic patients without heart failure versus the general population. Fig. 2 shows that the differences in arterial pressure were similar to those mentioned above. Therefore it is reasonable to think that even in the absence of heart failure, chagasic patients have lower pressures than the general population.

Chagasic patients with and without heart failure. There were no statistically significant differences between these two groups.

Chagasic patients and the general population related to ponderal groups. Fig. 3 shows the mean percentage deviation of each ponderal group when related to the mean of the general population (age and sex adjusted). The chagasic patients mean arterial pressures were always lower than the general population mean. On the other hand, the same ponderal groups of the general population show a rise in blood pressure with increasing ponderal index. It is worth mentioning that this blood pressure–weight relationship of the general population was not present in our chagasic population, as can be appreciated in Fig. 3.

Prevalence of hypertension. The percentage of systolic and diastolic hypertension in the general population was 9.4/11.6 for males and 13.3/12.8 for females, and among Chagasic patients it was 1.7/10.5 for males and 1.7/1.7 for females.

Discussion

Arterial hypotension in patients with Chagas disease has been reported in the medical literature.[-]

The first goal of this investigation was to determine whether chagasic patients had a lower arterial pressure level than the general population.

Fig. 1 shows that the mean systolic and diastolic pressures of chagasic patients were lower for any age or sex, than those of the general popula-

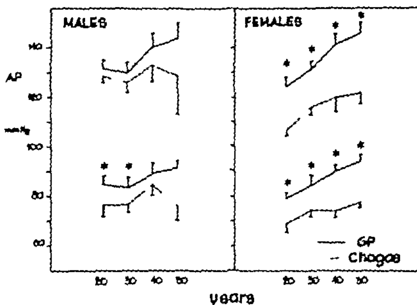


Fig. 2. Mean systolic and diastolic pressures for males and females for each ten year age group in the general population and in Chagasic patients without heart failure *Solid line* = general population, *broken line* = chagasic patients without heart failure. Symbols as in *Fig. 1*

tion. These differences were slightly greater among females and for the diastolic pressures.

The second goal was to know whether this diminished arterial pressure was produced by heart failure. Fig. 1 shows that pulse pressure tends to become greater because of the greater fall of the diastolic pressure. It is well known that heart failure diminishes pulse pressure Therefore it is hardly feasible to think that hypotension may only be due to a low cardiac output. To clarify this point, two other groups were made chagasic patients with and those without heart failure. Fig. 2 demonstrates that chagasic patients without heart failure have a lower pressure than the general population and there was no significant difference between chagasic patients with and those without heart failure This would make the hypothesis that heart failure be the only determining factor of hypotension in our chagasic patients very unlikely

The third goal was to investigate if arterial pressure among chagasic patients was conditioned by age sex and body weight as it is in the general population

Figs. 1 and 2 show that the slope of the age-pressure curve is smaller in chagasic patients than in the general population that is to say it is less dependent on the age factor than in the general population.

In our epidemiologic study of arterial hypertension in Córdoba, as in other reports, we also found that the mean female systolic pressures intersect those of the male, around the age of 35. This phenomenon was not observed among our chagasic patients, since the mean systolic pressures of women were always lower than those of men (Figs. 1 and 2)

Besides, the correlation between body weight and arterial pressure which is described in several epidemiologic studies of hypertension was not found in the chagasic patients we studied. For any age or sex, the mean systolic and diastolic pressures for each ponderal group of chagasic patients were lower than those of the general population (Fig. 3)

The consequence of the above mentioned facts, is that the prevalence of hypertension among chagasic patients is lower than in the general population.

It is difficult to explain the cause of this hypotension and it would be necessary to study each one of the different mechanisms that are actually known as determining factors of arterial pressure Some of them have already been studied. Cardiac output will not fall until the disease is well advanced and produces overt heart failure, as was demonstrated by Kuschnir and associates. *Therefore* total *peripheral resistance* should be low Unfortunately those studies did not measure arterial pressure and resistance.

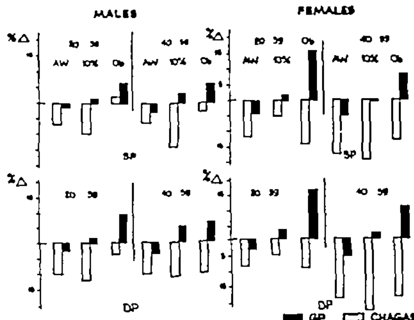


Fig. 3. Percentage deviation of systolic and diastolic pressures of each ponderal group in Chagasic patients (open bars) and in the general population (solid bars) when related to the general population mean (age and sex adjusted). Symbols: SP = systolic pressure; DP = diastolic pressure; $A.W.$ = average weight; 10% = from 10 to 25 per cent above the ideal weight; Ob = Obese (More than 25% the ideal weight).

On the other hand, in chagasic cardiomyopathy autonomic nervous system dysfunction has been described, manifested by alterations of the baroreceptor reflex,[18-1] Valsalva maneuver and the diving reflex.[21] Nevertheless, it is difficult to explain chagasic hypotension on these bases, since these alterations may be partially conditionated by heart failure and, besides, alterations of these reflexes do not necessarily produce hypotension. Other forms of arterial hypotension like idiopathic orthostatic hypotension, and Shy Drager syndrome[1] also have alterations of these autonomic reflexes, but the hypotension is mainly orthostatic, indicating a selective defect of the sympathetic nervous system. Chagasic patients do not have orthostatic hypotension to a degree enough to produce symptoms. Therefore, other factors should be mentioned.

Recently experimental studies have demonstrated that tissue damage in chronic Chagas disease probably occurs as a consequence of a lymphocyte-mediated immune mechanism[22] and/or immunoglobulins bound to the plasma membrane of the myocardial and endothelial cells.[21,23] It has also been demonstrated "in vivo" that the bound immunoglobulin in left ventricle myocardial biopsies is not only present in patients with overt heart failure but also in those who had no evidence of heart failure.[23] Furthermore, Sterin-Borda and colleagues[24] have revealed that the EVI antibody would act in/or near the β-adrenergic receptor of the auricular cells of rats, partially blocking the action of exogenous norepinephrine.

It is difficult to explain our findings of arterial hypotension in chronic chagasic non failing heart patients in the light of these recent investigations. Anyway what is important to emphasize is the fact that even in the absence of clinical evidence of heart failure or heart disease it is possible to have low arterial pressures; and we may speculate that these patients could be under the effects of the above-mentioned immunological effects, and that this, in a still unknown way might produce the hypotension.

Naturally this epidemiologic demonstration that Chagas disease induces a fall in arterial blood pressure, opens up new horizons for investigations that must be pursued in order to find a suitable explanation.

Summary

One hundred and fifteen chagasic patients were studied, who had positive Machado-Guerreiro complement fixation test and positive epidemiologic history. The mean age of the group was

39 ± 12 years and the male-female relation was 1/1. Only 29 had heart failure.

The chagasic population studied was compared with a previous study where we got the blood pressure curve of the general population in relation to age and sex (Medicina 31 393-415 1971)

The mean values of the systolic and diastolic pressures of chagasic men and women were significantly lower ($P < 0.05$) in each of the studied decades, than those of the general population, with a few exceptions.

The mean female systolic pressure did not surpass the mean male systolic pressure at the age of 30 as usually happens in the general population.

When the chagasic patients were subdivided into those with or without heart failure it was clear that there were no differences between these two groups and that patients without heart failure had significantly lower pressures than the general population.

When the chagasic population was subdivided into ponderal groups, the differences between the chagasic and general population increased. The blood pressure-weight relationship observed in the general population was not present in our chagasic patients. There were fewer hypertensive individuals among chagasic patients than in the general population.

The determining reasons for these observations are unknown and possible mechanisms are being discussed.

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Angiographic–echocardiographic correlation in mitral valve prolapse

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Since the initial description of the mitral valve prolapse syndrome in 1963, numerous clinical,[1-] echocardiographic,[-11] and angiographic[- -] studies have attempted to establish criteria for the diagnosis of this entity Although the incidence of this valvular abnormality in the general population is unknown, a recent claim that 43 per cent of patients undergoing cardiac catheterization had angiographic evidence of prolapse[20] *suggests that current criteria may not be sufficiently discriminatory* to exclude all normal mitral valves. The normal [21] and pathological [22] anatomy of the mitral valve has been extensively studied at necropsy but little description of its normal dynamic angiographic anatomy exists. A previous report has recommended criteria for the classification of angiographic variants of normal mitral valves,[23] but no independent validation was presented. This study correlates the angiographic and echocardiographic appearance of normal and prolapsing mitral valves, and demonstrates the elimination of false-positive angiographic diagnoses of mitral valve prolapse when the criteria of Spindola Franco and associates[23] are used.

Methods

To evaluate the accuracy of criteria established for the identification of normal and abnormal mitral valves, left ventriculograms and echocardiograms of patients undergoing cardiac catheterization at Montefiore Hospital and Medical Center between 1973 and 1977 were reviewed. Reports of 660 angiographic studies performed in 1973 and 1974 were studied. *Ventriculograms of* all patients with any suggestion of mitral valve abnormality and routine pre-catheterization echocardiograms were reanalyzed. One thousand twenty two ventriculographic and echocardiographic studies done since 1975 have been analyzed prospectively using previously established criteria.[24] [23] Patients were included in the study group only if both diagnostic angiographic and echocardiographic examinatio



Fig 1 Early diastolic frame of 35 mm. left ventricular cineangiogram from a patient without heart disease The fulcrum or point of attachment of the mitral leaflets to the mitral ring is clearly seen The fornix is the left ventricular myocardium between the fulcrum and papillary muscles *(PM)*. Because of the low fulcrum and absence of notching of the fornix, this mitral valve has the Type I configuration.

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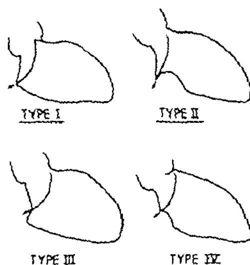


Fig. 2. Sketches of diastolic frames of left ventriculograms demonstrating the four mitral val configurations. The arrows identify the mitral valve fulcrums Types I and II have low fulcrums, but Type II has notched fornix Types III nd IV both ha high fulcrums, nd the fornix is also notched in Type IV

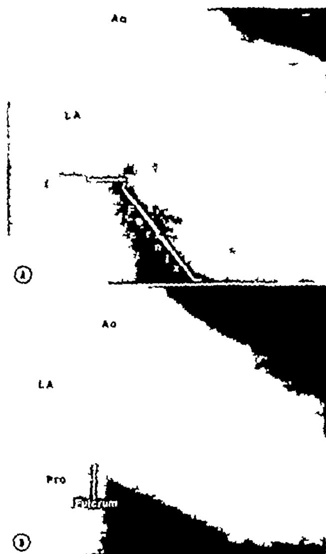


Fig 3 A and B A The low fulcrum and absence of notching in this diastolic frame make the mitr l valv configuration Type I Because of mitral regurgitation the outline of the left atrium (LA) is seen Ao = aortic root. B This systolic frame from the same patient as in Fig. 3A demonstrates movement of mitral valv tissue inferiorly and posteriorly beyond the fulcrum, resulting in mitral valv prolapse (Pro)

available. Echocardiograms and left ventriculograms were interpreted independently Only after separate review of the two diagnostic studies in all tients were the results pooled. Results of clini examination and/or phonocardiography were available for comparison.

Biplane angiographic studies were performed in the left anterior (LAO) and right anterior (RAO) oblique positions with a 6 inch Philips image intensifier and were recorded on 35 mm. film at 50 frames/second. Contrast medium (76 per cent sodium methyl-glucamine diatrizoate Renogra fin 76) was introduced into the left ventricular cavity through a retrogradely positioned arterial catheter by a Viamonte/Hobbs automatic injec tor at a rate of 10 to 16 ml./second for 3 seconds. Patients were positioned in either the supine or left lateral decubitus position for echocardiographic examination which was usually per formed on the day prior to cardiac catheteriza tion. A Hoffrel Ultrasonoscope (Model 101) with either a 2.25 MHz transducer focused at 7.5 cm. or an unfocused 2.0 MHz transducer was used for all studies. Echocardiograms as well as phonocardiograms processed by a piezoelectric crystal microphone (Type 53161, Kent Cambridge Ossining, N Y) were displayed on the oscilloscope of a Cambridge multichannel recorder and were permanently recorded on photographic paper

The configuration and dynamic changes of the mitral valve were determined by tracing the left ventriculographic image projected directly from the 35 mm. film. Identification of the mitral leaflets and their scallops, as well as the posteromedial and anterolateral commissures, was made in each study The mitral fulcrum and fornix were carefully delineated in each traced frame. The mitral fulcrum is the point of attach ment of the mitral leaflets to the annulus fibrosus (mitral ring) This point is clearly identified



Fig. 3C. Simultaneous echocardiogram and phonocardiogram demonstrate late systolic prolapse of the posterior mitral leaflet (PML) and a pansystolic murmur (SM), respectively. AML = anterior mitral leaflet.

during ventriculography in protodiastole as the interface between the unopacified blood rushing into the left ventricle and the contrast medium trapped in the recess between the mitral leaflets and ventricular endocardium (Fig. 1). The fornix of the left ventricle is that part of the heart between the insertion of the mitral leaflets at the annulus fibrosus and the plane of implantation of the papillary muscles.

In Fig. 2 the four patterns of normal mitral valve configuration as previously described[13] are outlined. Classification is dependent on the position of the mitral valve fulcrum in protodiastole in the right anterior oblique projection. Type I mitral valve is characterized by a low lying mitral fulcrum without notching of the ventricular fornix, whereas in Type II the fulcrum is also low but the fornix is notched. Types III and IV both have high mitral fulcrums, the former having a smooth and the latter a notched fornix. Normal systolic bulging (pseudoprolapse) of the mitral leaflets was recognized in some mitral valves, principally Type I, II, and III. Prolapse of the posterior mitral leaflet was considered to be present only if during systole there was posterior and inferior para annular displacement of the mitral valve leaflet beyond the level of the mitral valve fulcrum. Angiographic identification of prolapse of the posterior leaflet s posteromedial scallop was easily made in the right anterior oblique projection of the left ventriculogram.

Anatomic considerations support these angiographic criteria for the diagnosis of mitral valve prolapse. With chordal degeneration and elongation, normal apposition of the mitral leaflets during systole is lost. At the onset of ventricular contraction the mitral leaflets will be forced into the left atrium. Because of the leaflet attachment to the annulus, acceleration of blood and leaflets towards the atrium results in pivoting of the leaflets around the fulcrum producing posterior and inferior displacement of leaflet tissue beyond the annulus, thus permitting angiographic diagnosis. On the other hand, if chordal attachments and mitral leaflet apposition are normal, ventricular contraction produces only ballooning of the central leaflet area without para annular leaflet displacement, resembling a wind filled billowing sail.

Results

Of 660 angiographic studies performed before 1975, six reports suggested the presence of mitral valve motion abnormalities. Of these, four were examples of pseudoprolapse and represented variants of normal mitral valve anatomy and motion. One mitral valve was Type I, one was Type II, and two were Type III. All echocardiographic studies of the mitral valve in these four patients were normal. The remaining two left ventriculo-

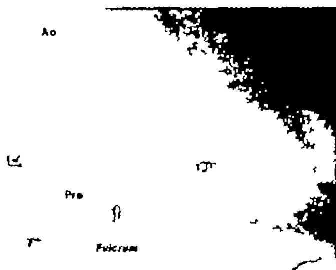


Fig 4A. Systolic frame of left ventricular angiogram demonstrating prolapse (Pro) of the mitral valve. The posteromedial commissural scallop of the posterior mitral leaflet extends posteriorly and inferiorly to the fulcrum



Fig 4B Simultaneous echocardiogram and phonocardiogram reveal mitral valve prolapse and a mid-systolic click (X)

grams showed one Type I and one Type II mitral valve configuration and true posterior leaflet prolapse, and this diagnosis was confirmed echocardiographically As seen in Fig. 3A identification of the mitral fulcrum and ventricular fornix in this angiographic frame shows this to be a Type I mitral valve. As systole begin the posteromedial commissural scallop of the posterior leaflet moves posteriorly and inferiorly to the mitral fulcrum. At end-systole a prominent prolapsing scallop is recognized (Fig 3B). This patient's mitral valve echogram demonstrates a late systolic prolapse (Fig. 3C).

Of the 1,022 left ventriculograms done since 1975 mitral valve prolapse was diagnosed angiographically in 19 patients using the above criteria. Seven had the Type I mitral valve configuration, whereas Type III was noted in nine. One patient had a Type II valve, and Type IV was documented in two patients. In Fig. 4A a mid-systolic

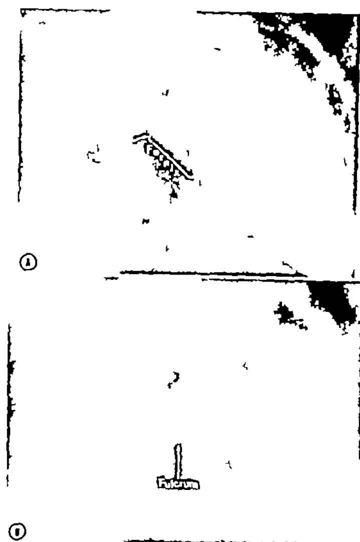


Fig 5. A and B. A, Early diastolic frame from left ventriculogram of pediatric patient with an atrial septal defect and partial anomalous pulmonary venous drainage The fulcrum is low and the fornix is notched, making this Type II mitral valve. B During systole there is normal bulging of the mitral leaflets, but no inferior displacement beyond the fulcrum, thus identifying this as pseudoprolapse. At surgery the mitral valve was normal, and no evidence of prolapse was noted. Therefore identification of the fulcrum as point of reference is mandatory before the diagnosis of mitral valve prolapse can be made

frame of the left ventriculogram of a patient with a Marfanoid habitus is presented. This patient had a Type I mitral valve. Again the mitral leaflet demonstrated angiographic prolapse as it moved posteriorly and inferiorly during systole. The diagnosis was supported by the echocardiogram (Fig. 4B).

In contrast to the ventriculographic frames presented in Figs 3 and 4 frames from the angiogram of one patient with congenital heart disease with Type II mitral valve (Fig 5) demonstrated pseudoprolapse. Although the leaflet bulged in systole, the tissue did not move inferiorly to the fulcrum. These two angiographic frames have been traced and appear in *panels A* and *B* of Fig. 6. The arrows point to the mitral valve fulcrum. As depicted by the dotted line in *panel B* mitral tissue does not extend inferiorly beyond the anatomic boundaries of its attachment to the annulus fibrosus during systole. Therefore, no prolapse is present. If a prolapse had been present, the pattern diagrammed in *panel C* would have been recorded. Here the mitral scallop extends posteriorly and inferiorly beyond the fulcrum The echocardiographic study in this patient showed the mitral valve to be very close

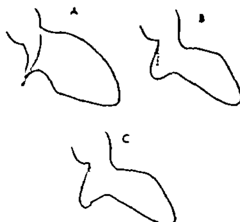


Fig. 6. *Panels A and B* represent artist's sketches of the diastolic and systolic frames shown in *Figs. 5A and B. The arrows indicate the fulcrum. Dotted lines* depict the usual configuration of the mitral valve in systole. However in some patients the mitral leaflet may bulge normally in systole without inferior displacement. In this patient *(panel B)* only leaflet bulging was noted. If prolapse had been present, the silhouette depicted in panel C would have been recorded. In this sketch mitral valve tissue is extending inferiorly and posteriorly to the fulcrum. Therefore the diagnosis of mitral valve prolapse is dependent on identification of the fulcrum.



Fig. 7A. Systolic frame from left ventricular angiogram of an 15-year-old woman with severe mitral regurgitation showing Type I mitral valve. During systole no prolapse of the posteromedial scallop is recognized. However the middle scallop *outlined by arrows* prolapses into the atrium. Therefore, in this patient examination of only the posteromedial scallop would have yielded a false-negative diagnosis of prolapse. Fortunately isolated prolapse of scallops other than the posteromedial one is uncommon. *PM* = papillary muscle.

to the posterior wall of the heart, but did not reveal any evidence of prolapse. The absence of mitral valve prolapse was confirmed by direct visualization at the time of surgery.

All 21 patients (two identified before 1975 and 19 between 1975 and 1977) with left ventriculograms demonstrating mitral valve prolapse also had echocardiographic evidence of prolapse. Phonocardiography demonstrated mid-systolic clicks and/or late systolic murmurs in 13 cases. Eight patients had holosystolic murmurs suggestive only of mitral regurgitation.

Since 1975 an additional three patients demonstrating typical echocardiographic prolapse have had cardiac catheterization. The prolapse was pansystolic in one and occurred late in systole in two patients. The diagnosis of mitral valve prolapse was supported by typical phonocardiographic abnormalities in two patients, while the remaining patient had only a holosystolic murmur. In these three patients the mitral valve morphology was classified as Type I, II and III respectively. The left ventriculographic studies, however did not support the diagnosis of prolapsing mitral valve.

Discussion

The diverse clinical manifestations and phonocardiographic and echocardiographic patterns in the mitral valve prolapse syndrome have generated great interest since the first comprehensive description of the entity. However angiographic description of the mitral valve motion abnormalities in this syndrome has received far less attention. Although Ranganathan and co-workers[1] have described angiographic features of the mitral valve prolapse syndrome, the lack of specific diagnostic criteria has caused others to overdiagnose the mitral valve abnormality and to greatly exaggerate its incidence in the patient population undergoing cardiac catheterization.[5, 6] Consequently it appeared necessary to establish definitive diagnostic angiographic criteria and to define potential causes for error in the ventriculographic evaluation of mitral valve motion.

Ranganathan and associates have stated that normal mitral valve leaflets may assume a convex configuration during systole, but that a distinct bulge into the left atrium is not apparent. However this distinction is vague, and faulty assessment of the degree of convexity or bulging may have

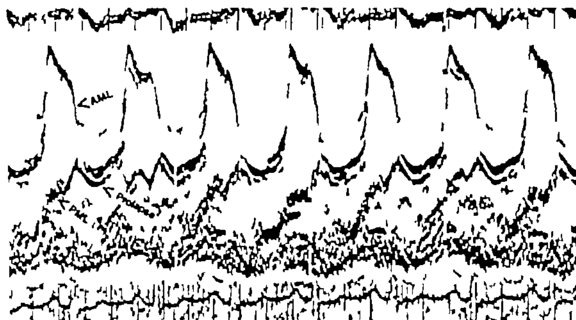


Fig. 7B. Echocardiogram shows systolic prolapse of the mitral valve.

caused the angiographer to overdiagnose mitral prolapse. In 1901 Luciani[29] showed that normal leaflet bulging did occur. After removing the left atrial wall and occluding the aorta of normal hearts, Luciani filled the left ventricular chamber with water until the mitral leaflets began to float closed. Then sudden and forceful injection of an additional few milliliters of fluid in the long axis of the ventricle produced complete closure of the mitral orifice with evident superior bulging of the leaflets. Furthermore Chiechi and associates have described normal billowing of mitral valve leaflets towards the left atrium at the time of cardiac surgery and the reports by Smith and co-workers,[30] Raizada and colleagues,[31] and Rurwitch and associates[32] document the frequent angiographic observation of end-systolic bulging of the mitral leaflets. Somerville and co-workers[33] have frequently noted angiographic evidence of mitral valve ballooning in patients with atrial septal defects. Although all cases were initially thought to represent prolapse, at the time of operation direct observation documented prolapse in only 18 per cent, thus confirming angiographic valve bulging as a frequent normal variant. It is not surprising that some degree of systolic mitral leaflet bulging might occur since the leaflet cross-sectional area is 1.5 to 2.0 times larger than that of the mitral orifice.[11]

The angiographic diagnosis of mitral valve prolapse as proposed here depends on the identification of the mitral valve fulcrum. Thus technically optimal radiologic studies must be available for analysis. Only if the mitral leaflet tissue is displaced posteriorly and inferiorly beyond the fulcrum during systole can the diagnosis of prolapse be justified. Systolic leaflet bulging is not sufficient. Because of the low fulcrum in Types I and II, the mistaken diagnosis of mitral prolapse is most likely to be made in these groups. In the initial study group of 100 normal left ventriculograms, 39 per cent of mitral valves were Type I, 9 per cent were Type II, 38 per cent were Type III, and 14 per cent were Type IV.[11] Therefore, if the fulcrum is not clearly identified, the potential for misdiagnosing mitral valve prolapse is present in nearly 50 per cent of normal angiograms.

The proposed criteria for the diagnosis of prolapsing mitral valve are actually based on analysis of the angiographic motion of the posteromedial commissural scallop in relation to the fulcrum. In the right anterior oblique projection it is this scallop which is most easily identified because it is not obscured by other opacified structures. Demonstration of prolapse of any of the other posterior leaflet scallops or anterior leaflet tissue would also be dependent upon identification of para annular displacement of tissue beyond the fulcrum. In the left anterior oblique projection para-annular displacement would be recognized by inferolateral movement of the

posterior leaflet's posteromedial scallop lateral movement of the middle scallop, and superior movement of the anterolateral scallop. Direction of displacement of the anterior leaflet would be similar to that of the posterior leaflet's anterolateral scallop. In Ranganathan and colleagues' material, virtually all patients with prolapse of some portion of the mitral valve had involvement of the posteromedial commissural scallop. Thu absence of prolapse of this scallop is strong evidence that the mitral valve is normal. Identification of the anterior leaflet and other posterior leaflet scallops is dependent upon technically [illegible] imal right and left anterior oblique angio[illegible] Although refinement of the diagnosis of [illegible] valve prolapse is possible if both mitral [illegible] ts and all scallops are identified, study of the [illegible] t the posteromedial scallop will suffice in [illegible] es

In [illegible] study echocardiographic and auscultatory [illegible] were used to support the diagnosis of mitral valve prolapse, since pathological data could not be obtained and supporting surgical data were available in only a few patients. It should be recognized, however that neither the echocardiogram nor the phonocardiogram can be accepted as the unequivocal basis for the diagnosis of this disorder Echocardiography may produce false positive results, silent prolapse has been described, and the echocardiogram may be normal in patients with abnormal auscultatory findings. Nonetheless, when carefully recorded the echocardiogram with supporting phonocardiogram does allow confident diagnosis of mitral valve prolapse.

Use of the present criteria for the diagnosis of mitral valve prolapse has eliminated false-positive angiographic studies. All patients with the angiographic diagnosis of prolapse also had diagnostic echocardiograms. These observations support the specificity of the proposed criteria and suggest that motion of normal mitral valves, even of the Types I and II configuration can successfully be distinguished from that of true prolapse.

All patients whose echocardiograms showed no evidence of posterior systolic displacement of the mitral leaflets also did not fulfill the angiographic requirements of prolapse. However three patients had positive echocardiograms in the face of normal angiograms as defined by the above criteria. In two of these patients the diagnosis of prolapsing mitral valve was supported by the characteristic auscultatory findings of mid systolic click and/or late systolic murmur while the other patient had a non-specific holosystolic murmur Although the proposed criteria have successfully eliminated false positive diagnoses, false negative (3 of 24) studies may occur Continued improvement of angiographic technique and image intensification will undoubtedly diminish the significance of this problem. One cause of a false-negative study may be the unusual occurrence of prolapse of a single scallop other than the posteromedial one. An angiographic frame from one of the patients with a positive echocardiogram (Fig. 7*B*) is presented in Fig. 7*A*. This patient had a Type I mitral valve. Systolic motion of the posteromedial scallop was entirely normal, and at no time was there inferior and posterior displacement beyond the mitral fulcrum. The initial left ventriculogram demonstrated only significant mitral regurgitation no other abnormality was observed. However a second angiogram was done after the degree of mitral insufficiency had been diminished by pharmacologic unloading of the left ventricle. As demonstrated in Fig. 7*A* it was now possible to identify an isolated prolapse of the middle scallop of the posterior leaflet. Thus in some situations unidentified prolapse of other posterior leaflet scallops or anterior leaflet tissue may be the cause of a "false-negative" angiographic study

The diagnosis of mitral valve prolapse can be established with angiography although echocardiography may be a more sensitive technique. Contrary to other reports,[illegible] it is apparent that the angiographic diagnosis of prolapse is not significantly more frequent than that based on clinical or echocardiographic grounds. Application of the criteria stressed in this report will help to reveal the true incidence of mitral valve prolapse in the patient population undergoing cardiac catheterization.

Summary

Although mitral valve prolapse is easily identified with echocardiography the angiographic diagnosis has been poorly understood. To determine relative specificity and sensitivity of recently established radiologic diagnostic criteria, prospective comparison of left ventriculograms

with echocardiograms and clinical observations in patients undergoing routine cardiac catheterization from 1975 to 1977 and retrospective review of earlier catheterization data have been performed. *Four types of normal mitral valve configurations were determined during protodiastole in the right* anterior oblique (RAO) projection of left ventriculograms by identifying the fulcrum, the point of attachment of the mitral leaflets to the annulus fibrosus, and the fornix that part of the left ventricular wall between the fulcrum and papillary muscles. Prolapse was present when mitral leaflet tissue extended inferiorly and posteriorly to the fulcrum during systole. Angiographic prolapse of the posteromedial commissural scallop of the posterior leaflet was diagnosed in RAO ventriculograms in 21 patients, approximately 1.9 per cent of the adult catheterization population. All of these patients also had positive echocardiograms. Three other patients had positive echocardiograms despite normal ventriculograms. In one of these three isolated prolapse of the middle commissural scallop of the posterior leaflet was *present. No patient with a normal mitral valve* echocardiogram had an abnormal ventriculogram. The proposed angiographic criteria for mitral valve prolapse have eliminated false-positive diagnoses, and permitted accurate identification in approximately 88 per cent of cases. Improved imaging and additional left ventriculographic projections will probably improve sensitivity. The frequencies of angiographic echocardiographic, and clinical diagnoses of mitral valve prolapse are not significantly different.

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Effects of ether anesthesia and surface-induced hypothermia on regional blood flow

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The relatively recent development of a technique based on the use of nonrecirculating radioactive microspheres has made possible the measurement of regional blood flow under experimental conditions. Regional blood flow is of particular importance during induced hypothermia procedures because a knowledge of the total and organ blood flow may provide a basis for comparing various empirically developed cooling techniques and improving the clinical result of currently applied techniques.

As an initial study we elected to examine regional blood flow and the distribution of cardiac output during the cooling phase utilizing the method of surface-induced hypothermia developed and applied clinically at this institution.

Methods

Experimental procedure Seven monkeys *(macaca mulatta)* weighing from 4 to 7 kilograms were studied. Under ketamine anesthesia (100 mg. intramuscularly) catheters were placed aseptically into the inferior vena cava and abdominal aorta via left iliac vessels, and into the left ventricle through the left common carotid artery After catheterization each monkey was placed in a primate restraining chair for a period of three days to permit recovery from surgery All catheters were continuously infused (0.5 ml./hr) with 0.3 per cent heparinized saline solution to maintain patency

One hour prior to an experiment, atropine (0.0? mg./Kg., intramuscularly) and methohexital (intravenously in minimal amount to induced hypnosis) were administered and the animal was placed in the supine position within a sound protected box. The catheters were connected to Statham P23 pressure transducers placed at the mid thoracic level outside the box, thus enabling all measurements, infusion and blood sampling to be performed with minimal disturbance to the animal. Heparin (2000 units intravenously) was injected before the first blood sampling for cardiac output measurement to prevent blood clotting.

Following control determinations, animals were anesthetized and prepared for cooling. Surface cooling was carried out with the method we have previously described. Briefly the method includes the use of deep (third plane, third stage) ether anesthesia, artificial ventilation maintained at normal levels for normothermia so as to gradually induce respiratory alkalosis during cooling, and the administration of 10 c.c./Kg. low molecular weight Dextran (10 per cent in D W) at rate of 1 ml./Kg./ C. drop in temperature between 35 and 25 C. during cooling.

At the end of each experiment the animal was exsanguinated and the major organs were removed, weighed and placed in plastic vials to facilitate counting of radioactivity The remainder of the body mainly skin, muscle fat and bones, was ashed and a 20 per cent aliquot of the

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mixed ash was also placed in vials for counting.

Data collection and analysis Arterial central venous, and left ventricular pressure and ECG (Lead II) were continuously recorded on a Hewlett Packard model 7788A recorder with appropriate amplifiers. Cardiac outputs were determined in duplicate by the dye-dilution technique. Indocyanine green was injected into the left ventricle and blood was withdrawn at a constant rate with a Harvard pump from the catheter in the abdominal aorta and passed through a Waters X-302 densitometer All blood was reinfused after the dye curve had been obtained. Immediately after each cardiac output determination and microsphere injection, arterial blood samples were analyzed for pH PCO and PO with a Radiometer model 27 blood gas analyzer Temperatures of the pH and blood gas electrodes were preadjusted to sampling temperature in order to eliminate temperature correction errors. Blood levels of ether were assayed by gas chromatography Blood samples withdrawn were replaced with fresh blood drawn from a donor monkey Rectal and esophageal temperatures were monitored continuously with Yellow Springs thermistor probes.

The distribution of blood flow was determined by injecting a suspension of nuclide-labeled microspheres (50 μm diameter) containing 1 to 3 × 10" counts/minute of isotope into the left ventricle. The suspension was prepared by mixing microspheres (3M Company) in 20 per cent Dextran with a vortex (Scientific Products Co) vibrating mixer The following nuclide-labeled microspheres were used "Sc, Nb 'Sr Cr and Ce, enabling five separate blood flow determinations in the same animal Hemodynamic control determinations and the first microsphere injection were done at normothermia in unanesthetized animals. When a steady state of third plane, third stage anesthesia was reached just prior to the onset of cooling, hemodynamic measurements were repeated along with a second injection of microspheres. Subsequent measurements and microsphere injections were done at 30 25 and 20 C rectal temperature during cooling.

The radioactivity of each vial containing tissue or ash was counted using a Packard NaI scintillation counter Model 9011 Energy distribution patterns were recorded on a Packard Pulse-Height Analyzer with 1,024 channels. Since each of the nuclides used has a gamma emission spectrum with a characteristic shape and energy level the amount of radioactivity from each vial, and hence each organ was determined. The composite spectra of all five nuclides for each vial were stored on magnetic tape and process by a PDP 15 computer to give individual counts of all isotopes in each vial.

The fraction of cardiac output to each organ was calculated as the amount of each nuclide s radioactivity in that organ divided by the total body count for that nuclide. Blood flow to each organ was calculated as fraction of the cardiac output times the cardiac output from the dye dilution curves obtained immediately prior to the injection of that particular nuclide. Peripheral and organ resistances were calculated by dividing the difference between mean arterial pressure and mean central venous pressure (Torr) by flow (L./minute)

The raw data were tabulated and processed to yield the means and standard error of means for each parameter Statistical significance was confirmed or denied where appropriate with the Student s paired t test. Changes were considered significant when the value for P was less than 0 05

Results

Hemodynamic parameters. All animals were anesthetized and cooled uneventfully with changes in hemodynamic and blood gas parameters qualitatively similar to those previously observed in dogs and infants. As body temperatures declined to 20° C., there was a progressive descrease in heart rate and prolongation of the P R, QRS, and QT intervals. All animals remained in normal sinus rhythm except with occasional ventricular premature contractions which were due to the stimulation of the left ventricular wall by the catheter These ECG observations in the monkey are in agreement with those in infants undergoing surface-induced deep hypothermia for open heart surgery Just prior to the onset of cooling under conditions of deep ether anesthesia, cardiac output and stroke volume were significantly reduced, whereas heart rate did not differ from unanesthetized control values.

During cooling to 30° C cardiac output declined to approximately 74 per cent of the unanesthetized control while heart rate and mean

Table 1 Systemic hemodynamic parameters and blood gases

	Control	*Ether Anesthesia*			
	37°C	*37°C*	*30°C*	*25°C*	*20°C*
HR (beats/min.)	183 ± 9	182 ± 6	129 ± 3* §	84 ± 3 §	53 ± 3 §
MAP (Torr)	117 ± 4	79 ± 6*	60 ± 4 *‡	60 ± 4 §	37 ± 5 **§
CVP (Torr)	4.5 ± 0.9	4.9 ± 0.9	3.6 ± 0.8	6.1 ± 0.9*†	7.3 ± 1.2*†
CO (mL/min./Kg.)	257 ± 31	225 ± 23	191 ± 26*	104 ± 20 **§	64 ± 8* §
SV (mL/Kg.)	1.44 ± 0.20	1.15 ± 0.13	1.46 ± 0.19†	1.25 ± 0.23	1.05 ± 0.17
TPR (Torr/L./min.)	53 ± 6	64 ± 8	52 ± 5	74 ± 10†	109 ± 23†
pH	7.51 ± 0.02	7.54 ± 0.03	7.61 ± 0.05	7.67 ± 0.07*†	7.66 ± 0.06*†
PaO_2 (Torr)	102 ± 6	427 ± 31	437 ± 24	441 ± 30*	451 ± 35*
$PaCO_2$ (Torr)	31 ± 2	29 ± 2	17 ± 1 *‡	15 ± 3**‡	16 ± 3*‡
Hematocrit (%)	32 ± 1	33 ± 1	24 ± 2* §	23 ± 1 §	24 ± 1 **§
Blood ether Conc. (%)	0	3.62 ± 0.43	3.37 ± 0.25	2.48 ± 0.33†	2.24 ± 0.37‡

*The values are means and standard errors of the means. and † denote $p \leq 0.05$, and ‡ denote $p \leq 0.01$ and § denote $p \leq 0.001$. The statistical significances are shown as asterisks ( ) when the results are compared to that of unanesthetized control values. The statistical significances are shown in daggers (†) when the results are compared to that of anesthetized pre-cooling values.
HR = heart rate, MAP = mean arterial pressure, CVP = central venous pressure, CO = cardiac output, SV = stroke volume, TPR = total peripheral resistance.

arterial pressure were at 71 per cent and 51 per cent, respectively. The mean stroke volume was not statistically different from that of the unanesthetized control.

At 20 C, cardiac output had decreased to 21 per cent of unanesthetized control, corresponding heart rate and mean arterial pressure percentages were 29 per cent and 32 per cent, respectively. Mean stroke volume was unchanged at 20 C with large individual variation.

The use of normoventilation for normothermia with ether in pure oxygen resulted in a gradually increasing pH, decreasing $PaCO_2$, and high PaO_2. Hematocrit decreased during cooling to 30 C and remained stable thereafter. The above information is summarized in Table I.

Total vascular and organ resistance Total vascular resistance and individual organ resistances were subject to wide individual variations. Fig. 1 graphically presents total vascular and organ resistances with *(A)* the unanesthetized control value as the reference value (i.e., 100 per cent) and *(B)* the anesthetized precooling value as the reference value (i.e., 100 per cent). The trends thus indicated suggest that following the induction of anesthesia, cerebral vascular resistance increased, coronary and carcass vascular resistance did not change, and hepatic arterial, splanchnic, and renal resistances decreased. With the addition of surface cooling, coronary resistance was unchanged and cerebral and hepatic arterial resistances decreased slightly as the temperature fell to 30 C while splanchnic, renal, and carcass resistances decreased to a greater degree. Cooling from 30° C to 20° C resulted in relatively parallel increases of vascular resistance throughout the body. When compared to anesthetized pre-cooling values (Fig. 1*B*) all resistances increased to levels in excess of 150 per cent at 20 C.

Changes in distribution of cardiac output. Following induction of anesthesia to the level required for cooling, the fraction of cardiac output delivered to the heart, brain, kidneys or liver was not significantly altered. Splanchnic output fraction increased by 10 per cent of total output, while carcass output fraction decreased by a proportionate amount. During cooling to 20 C., output fractions to the various organs did not fluctuate to a statistically significant degree from precooling anesthetized values. However, when compared to the unanesthetized control, brain and carcass fractions decreased while the splanchnic fraction increased significantly (Table II).

Changes in absolute organ flow An increased blood flow to the splanchnic arterial system and decreased flows to the remainder of the body was observed following the induction of anesthesia. During cooling, all flows appeared to decrease in a fashion parallel to the decrease in total cardiac output (Table II). At 20 C, flow to the brain was about 18 per cent of unanesthetized control, and 20 per cent of the anesthetized pre-cooling value.

mixed ash was also placed in vials for counting.

Data collection and analysis. Arterial, central venous, and left ventricular pressure and ECG (Lead II) were continuously recorded on a Hewlett Packard model 7788A recorder with appropriate amplifiers. Cardiac outputs were determined in duplicate by the dye-dilution technique. Indocyanine green was injected into the left ventricle and blood was withdrawn at a constant rate with a Harvard pump from the catheter in the abdominal aorta and passed through a Waters X-302 densitometer. All blood was reinfused after the dye curve had been obtained. Immediately after each cardiac output determination and microsphere injection, arterial blood samples were analyzed for pH, PCO_2, and PO_2 with a Radiometer model 27 blood gas analyzer. Temperatures of the pH and blood gas electrodes were preadjusted to sampling temperature in order to eliminate temperature correction errors. Blood levels of ether were assayed by gas chromatography. Blood samples withdrawn were replaced with fresh blood drawn from a donor monkey. Rectal and esophageal temperatures were monitored continuously with Yellow Springs thermistor probes.

The distribution of blood flow was determined by injecting a suspension of nuclide-labeled microspheres (50 μm diameter) containing 1 to 3×10^6 counts/minute of isotope into the left ventricle. The suspension was prepared by mixing microspheres (3M Company) in 20 per cent Dextran with a vortex (Scientific Products Co.) vibrating mixer. The following nuclide-labeled microspheres were used: Sc, Nb, Sr, Cr and Ce enabling five separate blood flow determinations in the same animal. Hemodynamic control determinations and the first microsphere injection were done at normothermia in unanesthetized animals. When a steady state of third plane, third stage anesthesia was reached just prior to the onset of cooling, hemodynamic measurements were repeated along with a second injection of microspheres. Subsequent measurements and microsphere injections were done at 30, 25, and 20° C rectal temperature during cooling.

The radioactivity of each vial containing tissue or ash was counted using a Packard NaI scintillation counter Model 9011. Energy distribution patterns were recorded on a Packard Pulse-Height Analyzer with 1,024 channels. Since each of the nuclides used has a gamma emission spectrum with a characteristic shape and energy level, the amount of radioactivity from each vial, and hence each organ, was determined. The composite spectra of all five nuclides for each vial were stored on magnetic tape and processed by a PDP 15 computer to give individual counts of all isotopes in each vial.

The fraction of cardiac output to each organ was calculated as the amount of each nuclide's radioactivity in that organ divided by the total body count for that nuclide. Blood flow to each organ was calculated as fraction of the cardiac output times the cardiac output from the dye-dilution curves obtained immediately prior to the injection of that particular nuclide. Peripheral and organ resistances were calculated by dividing the difference between mean arterial pressure and mean central venous pressure (Torr) by flow (L./minute).

The raw data were tabulated and processed to yield the means and standard error of means for each parameter. Statistical significance was confirmed or denied where appropriate with the Student's paired t test. Changes were considered significant when the value for P was less than 0.05.

Results

Hemodynamic parameters. All animals were anesthetized and cooled uneventfully with changes in hemodynamic and blood gas parameters qualitatively similar to those previously observed in dogs and infants. As body temperatures declined to 20° C., there was a progressive decrease in heart rate and prolongation of the P-R, QRS, and QT intervals. All animals remained in normal sinus rhythm except with occasional ventricular premature contractions which were due to the stimulation of the left ventricular wall by the catheter. These ECG observations in the monkey are in agreement with those in infants undergoing surface-induced deep hypothermia for open-heart surgery.[11] Just prior to the onset of cooling under conditions of deep ether anesthesia, cardiac output and stroke volume were significantly reduced, whereas heart rate did not differ from unanesthetized control values.

During cooling to 30° C., cardiac output declined to approximately 74 per cent of the unanesthetized control while heart rate and mean

Table I Systemic hemodynamic parameters and blood gases

	Control	*Ether Anesthesia*			
	37°C	*37°C*	*30°C*	*25°C*	*20°C*
HR (beats/min.)	183 ± 9	182 ± 6	129 ± 5* §	84 ± 3* §	53 ± 3 §
MAP (Torr)	117 ± 4	78 ± 6	60 ± 4 *‡	60 ± 4* §	37 ± 5 §
CVP (Torr)	4.5 ± 0.9	4.9 ± 0.9	3.6 ± 0.8	6.1 ± 0.9 †	7.3 ± 1.2*†
CO (mL/min./kg.)	257 ± 31	225 ± 23	191 ± 26*	104 ± 20* §	54 ± 8 §
SV (mL/Kg.)	1.44 ± 0.20	1.15 ± 0.13	1.48 ± 0.19†	1.26 ± 0.23	1.08 ± 0.17
TPR (Torr/L./min.)	83 ± 6	64 ± 8	52 ± 5	74 ± 10†	109 ± 22†
pH	7.51 ± 0.02	7.54 ± 0.03	7.61 ± 0.05	7.67 ± 0.0**†	7.66 ± 0.06*†
PaO_2 (Torr)	102 ± 8	427 ± 31	437 ± 24	441 ± 20*	451 ± 23*
$PaCO_2$ (Torr)	31 ± 2	29 ± 2	17 ± 1 *‡	15 ± 3* ‡	16 ± 3*‡
Hematocrit (%)	33 ± 1	32 ± 1	24 ± 2 §	23 ± 1 §	24 ± 1 §
Blood ether Conc. (%)	0	3.52 ± 0.43	3.37 ± 0.35	2.45 ± 0.39†	2.24 ± 0.27‡

*The values are means and standard errors of the means. and † denote p ≤ 0.05, and ‡ denote p ≤ 0.01, ** and § denote p ≤ 0.001. The statistical significances are shown as asterisks ( ) when the results are compared to that of unanesthetized control values. The statistical significances are shown as daggers (†) when the results are compared to that of anesthetized pre-cooling values.
HR = heart rate, MAP = mean arterial pressure; CVP = central venous pressure, CO = cardiac output, SV = stroke volume; TPR = total peripheral resistance

arterial pressure were at 71 per cent and 51 per cent, respectively. The mean stroke volume was not statistically different from that of the unanesthetized control.

At 20° C. cardiac output had decreased to 21 per cent of unanesthetized control, corresponding heart rate and mean arterial pressure percentages were 29 per cent and 32 per cent, respectively. Mean stroke volume was unchanged at 20 C with large individual variation.

The use of normoventilation for normothermia with ether in pure oxygen resulted in a gradually increasing pH decreasing PaCO and high PaO_2. Hematocrit decreased during cooling to 30 C and remained stable thereafter. The above information is summarized in Table I.

Total vascular and organ resistance Total vascular resistance and individual organ resistances were subject to wide individual variations. Fig. 1 graphically presents total vascular and organ resistances with *(A)* the unanesthetized control value as the reference value (i.e. 100 per cent), and *(B)* the anesthetized precooling value as the reference value (i.e. 100 per cent). The trends thus indicated suggest that following the induction of anesthesia, cerebral vascular resistance increased coronary and carcass vascular resistance did not change, and hepatic arterial, splanchnic, and renal resistances decreased. With the addition of surface cooling, coronary resistance was unchanged and cerebral and hepatic arterial resistances decreased slightly as the temperature fell to 30 C., while splanchnic, renal, and carcass resistances decreased to a greater degree. Cooling from 30 C to 20 C resulted in relatively parallel increases of vascular resistance throughout the body. When compared to anesthetized pre-cooling values (Fig. 1B) all resistances increased to levels in excess of 160 per cent at 20 C.

Changes in distribution of cardiac output. Following induction of anesthesia to the level required for cooling, the fraction of cardiac output delivered to the heart, brain, kidneys or liver was not significantly altered. Splanchnic output fraction increased by 10 per cent of total output, while carcass output fraction decreased by a proportionate amount. During cooling to 20 C., output fractions to the various organs did not fluctuate to a statistically significant degree from precooling anesthetized values. However when compared to the unanesthetized control, brain and carcass fractions decreased while the splanchnic fraction increased significantly (Table II).

Changes in absolute organ flow An increased blood flow to the splanchnic arterial system and decreased flows to the remainder of the body was observed following the induction of anesthesia. During cooling, all flows appeared to decrease in a fashion parallel to the decrease in total cardiac output (Table II). At 20 C flow to the brain was about 18 per cent of unanesthetized control, and 20 per cent of the anesthetized pre-cooling value.

Table II Percentages of cardiac output (% $\dot{Q}$) and absolute blood flows (mL/min./100 g. tissue weight) to various organs and tissues

	Control	*Ether anesthesia*			
	37°C	*37°C*	*30°C*	*25°C*	*20°C*
CO (mL/min.)	1357 ± 108	1118 ± 80	1002 ± 105	641 ± 76* ‡	298 ± 36 ‡
Heart % $\dot{Q}$	5.8 ± 0.7	6.1 ± 1.1	4.6 ± 0.5	4.5 ± 0.6	4.2 ± 0.8
mL/min./100 g.	347 ± 38	315 ± 62	222 ± 41	120 ± 31 †	54 ± 6 *‡
Brain % $\dot{Q}$	4.6 ± 0.6	4.7 ± 1.1	3.4 ± 0.4	3.3 ± 0.5	3.9 ± 0.6*
mL/min./100 g.	63 ± 7	55 ± 14	34 ± 4	17 ± 2 †	11 ± 2 *‡
Kidneys % $\dot{Q}$	14.3 ± 0.8	15.7 ± 2.4	15.9 ± 1.6	18.4 ± 1.9	17.2 ± 1.7
mL/min./100 g.	694 ± 91	623 ± 119	547 ± 67	350 ± 67* †	177 ± 25 ‡
Liver % $\dot{Q}$	6.3 ± 1.0	7.1 ± 0.8	6.2 ± 1.0	6.8 ± 1.3	6.7 ± 1.4
mL/min./100 g.	52 ± 12	48 ± 8	35 ± 7	20 ± 6*	10 ± 2*†
Splanchnic % $\dot{Q}$	22.1 ± 2.5	32.0 ± 5.3	32.2 ± 1.3	30.7 ± 2.0*	32.3 ± 2.0*
mL/min./100 g.	71 ± 15	83 ± 20	73 ± 10	38 ± 7 ‡	21 ± 3 ‡
Carcass % $\dot{Q}$	51.3 ± 3.4	40.3 ± 5.2	43.2 ± 2.9	43.1 ± 3.6	41.0 ± 3.7*
mL/min./100 g.	16 ± 2	10 ± 4	10 ± 1	5 ± 1 *†	3 ± 0.4 *‡

*The symbols for statistical analyses are described in Table I.

Comparable flow to other organs at 20° C were heart—16 per cent and 17 per cent liver—19 per cent and 21 per cent splanchnic—30 per cent and 25 per cent kidneys—26 per cent and 28 per cent and carcass—19 per cent and 30 per cent.

Discussion

Blood flow distribution during hypothermic procedures has remained obscure because of the lack of a comprehensive non invasive detection system. The development of a technique based upon the use of radioactive microspheres of known size undoubtedly has and will continue to provide information that can improve clinical results. However as is often the circumstance with new methodology technical considerations arise which are noteworthy because of their influence on experimental results.

Several investigators have discussed the importance of microsphere characteristics and observed that size determines whether or not complete passage through the vascular system with subsequent recirculation will occur and where in the peripheral system the spheres will lodge (arteriole, capillary etc) It is also reasonable to believe that spheres of inappropriate size and density will not be distributed proportionally to blood flow These and other aspects of microsphere methodology are well reviewed by Heymann and associates. We elected to use relatively large (50 μm) microspheres because little is known about peripheral vascular caliber or the caliber of arteriovenous anastomoses under hypothermic conditions. Also since others have used microspheres of this size during hypothermia, we felt results could be reasonably compared by eliminating size as an additional variable. Interestingly it seems theoretically possible to use microspheres of graduated sizes as a means of calibrating the peripheral vasculature, although such studies have yet to be reported.

Other technical problems include those of mixing, and the number of microsphere injections that can be done during the course of a single experiment. Mixing is more complete with left atrial injections, however retrograde catheterization and left ventricular injections are often more practical. Furthermore, it has been reported that good mixing of 50 μm microspheres does occur with left ventricular injections in rhesus monkeys.

Currently only about five separate microsphere injections can be done during a single experiment because of the difficulty in identifying and quantifying the various overlapping radioactive spectra of available isotopes. For these reasons most studies utilize widely spaced data collection points. We are aware from previous studies that the induction of surface hypothermia to temperatures below 20 C is a dynamic process and that observations should be made at least every five degrees centigrade throughout the proce-

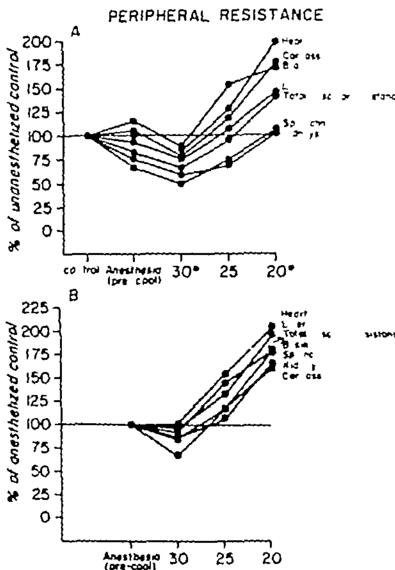


Fig. 1. Total vascular and individual organ resistances plotted with the unanesthetized control value as the 100 per cent value (A), and the anesthetized pre-cooling value as the 100 per cent value (B).

dura.[14] Thus, this initial series exclusively evaluates blood flow and flow distribution during the cooling phase only.

Most previous studies (including our own) report changes in physiologic parameters relative to an anesthetized normothermic control. The current study also provides a non-anesthetized control so that the effects of deep ether anesthesia in 100 per cent O_2 per se may be evaluated. Briefly, the trends included a 10 to 15 per cent reduction in total cardiac output, a decreased output fraction to the carcass, an increased output fraction to the splanchnic circulation, decreased flows to all regions except the splanchnic circulation which increased, and a reduction in vascular resistance. Remarkably, the addition of cooling resulted in no statistically significant change in output fractions during cooling to 20° C. While this is due, in part, to large variances related to the technical aspects of the measurement procedure, the suggestion remains that deep ether anesthesia provides a stable regional flow pattern that is only minimally altered by cooling to 20° C. Consequently, individual organ flows closely parallel changes in total cardiac output during cooling.

These findings are at variance with those reported by other investigators. Kawashima and colleagues, using dogs, reported decreased output fractions to the brain, liver, kidneys, and adrenals

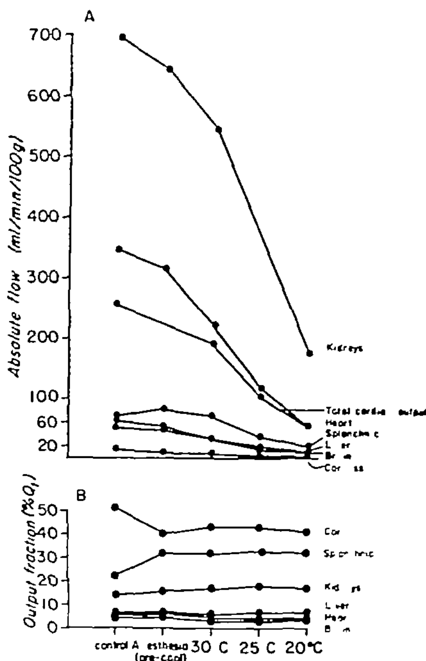


Fig 2. Absolute flow (A) tend to decrease during cooling in parallel with the reduction of cardiac output. Output fraction data (B) suggests that flow is redistributed from carcass to splanchnic vascular beds as the result of anesthesia. During cooling, output fractions do not change significantly

and increased fractions to the small intestine and muscle at 24 C when compared to anesthetized pre-cooling values. These differences may be related to differences in anesthetic management since Kawashima and colleagues used nitrous oxide-pancuronium anesthesia with phenoxybenzamine alpha blockade. Rudy and co-workers reported decreased brain and kidney output fractions and an increased muscle fraction at 15 C during constant-output perfusion cooling using phencyclidine–morphine anesthesia. Further research should be done to establish (1) comparisons of regional distribution and individual organ blood flows between the anesthetic regimens currently in clinical use, (2) correlations between regional flow and morbidity and mortality (3) the validity of the hypothesis that deep ether anesthesia administered by the technique described herein stabilizes output distribution, and (4) that these distribution patterns may be main

tained in the presence of artificial support of total flow so as to permit cooling to lower temperatures and ultimately better clinical results following longer usable periods of complete circulatory arrest.

The consensus appears to be that total periph eral resistance is increased as body temperature decreases, regardless of the method of cooling or anesthetic employed. Previous work with our technique using dogs is in agreement in that peripheral resistance began to rise within a few degrees of the onset of cooling.[18] In the current study an initial decrease was observed between the onset of cooling and 30 C. Thereafter total vascular and individual organ resistances rose relatively linearly with the fall in temperature

The inclusion of an unanesthetized data point again reveals the need to consider the effects of the anesthetic *per se* When peripheral resistance data were evaluated as a per cent change from the commonly used anesthetized normothermic control, the values during cooling in this study were much greater at 20° C. than when compared to the unanesthetized state. An unanesthetized control is therefore very important when dealing with potent vasoactive anesthetics or drugs.

Within the confidence limits of these data, the per cent change of individual organ and total vascular resistances shows an increase in a direct relationship to the fall in temperature between 30° and 20° C On the other hand if per cent changes in organ resistances are compared with the unanesthetized vs the anesthetized data points as the 100 per cent value, it becomes apparent that ether as given in this study can alter individual organ resistances during cooling by changing the reference points. Possibly other agents or lighter anesthetic levels with ether would result in different resistance patterns between the various organs or allow such patterns to be altered during the cooling course.

Vascular resistance changes during cooling have been a source of much discussion because of the milieu of many potentially influencing factors. Gordon has suggested that flow resistance may be expressed as.

$$\text{Resistance} \propto \text{viscosity} \times \text{vascular resistance}$$

By applying an empiric formula recently devel oped in this laboratory viscosity may be approx imated from measured temperature and hemato-

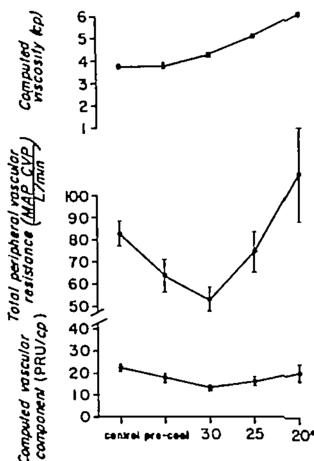


Fig 3. When computed blood viscosity in centipoises (CP) and total peripheral vascular resistance in Woods peripheral resistance units *(PRU)* are analyzed by the method described in the text, the resultant vascular component of total resistance appears not to increase during cooling to 20° C. This suggests that total peripheral vascular resistance increases during cooling due to blood viscosity rather than to vascular changes.

crit (unpublished data) The result is a viscosity value at a shear rate similar to that in major arterial vessels. When the ratio of total resistance/viscosity is plotted (Fig. 3) we observe essentially no difference between control and the value obtained at 20° C. This suggests that the purely vascular component of the resistance increase during cooling is relatively small and that most of the increase in total resistance is due to a rising viscosity

Verification of these observations would allow separation of the two components of total v lar resistance, which should be useful in co ing various cooling techniques and in the d future studies involving the effects of r manipulations under hypothermic con

Summary

Regional blood flow and distribution of cardiac output (CO) were evaluated by the radioactive microsphere technique in seven rhesus monkeys prior to anesthesia, following the induction of deep ether anesthesia and throughout the cooling course during surface-induced hypothermia to temperatures of 20 C As given deep ether anesthesia alone significantly decreased CO 10 per cent to 15 per cent and output fraction (Qt) was decreased to the carcass, increased to the splanchnic circulation (although not statistically significant) and unchanged to other organs, while total vascular (TVR) and organ resistances were reduced. With the addition of cooling, CO progressively decreased Individual organ Qt s, however did not change from anesthetized normothermic values thus organ flows decreased parallel to the reduction of CO as cooling progressed. TVR and organ vascular resistances increased to levels in excess of 150 per cent of anesthetized precooling values, apparently as the result of viscosity rather than vascular changes.

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Coronary arteriography in acute transmural myocardial infarction

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Coronary arteriography is widely performed but is often regarded as contraindicated during the acute phase of myocardial infarction. The angiographic images of the coronary arteries after a recent transmural infarction are therefore not very well known. Coronary angiographic studies in recent myocardial infarction have been performed by Begg and associates in 51 patients, five of whom were within the first 10 hours after infarction and by Miller[2] in nine cases. More recently Williams and colleagues assessed the part played by the collateral circulation in 20 patients with recent acute infarctions, on the average of 15 days after the acute incident. There are a large number of autopsy reports, but we have very little information on the state of the coronary arteries in survivors. It was for this reason that we undertook a systematic prospective study of 106 cases of recent acute transmural infarction. The goal of this study was to determine the state of the coronary system with the hope of establishing a prognosis and detecting possible correctable lesions in the vessels. The results suggest that the examination can be performed without serious risk in patients with recent myocardial infarction prior to their discharge from the hospital. The lesions that were found usually involved two or three vessels.

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Materials and methods

We studied 106 patients with recent acute myocardial infarction, admitted to the Coronary Care Unit of the Division of Cardiology in the University Hospital of Lille. The diagnosis of acute transmural myocardial infarction was established by a history of typical angina pain lasting for more than 20 minutes, appearance of a new Q wave of 0.04 sec. duration and progressive changes in the ST segment and T waves, a simultaneous rise in creatinine phosphokinase (CPK) and serum glutamic-oxaloacetic transaminase (SGOT) above the upper limits of normal. Patients meeting these criteria were divided in two groups according to the location of infarct established by the electrocardiogram

1 Posterior infarction—this word included inferior infarction, the "true posterior infarction and the postero-inferior infarcts. This group included 61 patients with a mean age of 50.6 ± 8.6 years (Range 31 to 68 years).

2. Anterior infarction including anteroseptal, anterolateral, and apical infarcts. In this group were 45 patients with a mean age of 50.2 ± 8.7 years (Range 30 to 67 years)

Left heart catheterization was performed by the percutaneous femoral technique. Left ventricular and aortic pressures were recorded. Cardiac output was determined in duplicate using the dye dilution technique. Single plane left ventriculog

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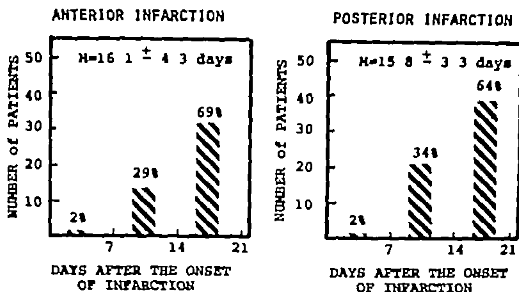


Fig. 1 Date of coronary arteriography

Table I Left anterior descending artery (LAD) in anterior infarction

	No.	%	Distal part of LAD			
			*Without DR**	*Very slight DR*	*Slight DR*	*Good DR*
Totally occluded	20	44	17		3	
Narrowing 75-95%	16	36		4		11
Narrowing 50-75%	8	18		1		7
Normal	1	2				

DR = distal runoff

raphy was performed in the 30 degree RAO projection using 35 mm film taken at 50 frames/second and a Philips 9/5 image amplifier system. Selective coronary arteriography was performed by the Judkins technique using Bourassa s catheters. The left coronary artery was examined with five projections right anterior oblique (RAO 30 degrees, RAO 15 degrees associated with 15 degrees of caudal angulation, left anterior oblique (LAO) 55 degrees associated with 25 degrees of cranial angulation, lateral (90 degrees) and LAO (110 degrees)

The right coronary artery (RCA) was studied with four projections LAO 50 degrees associated with 10 degrees of cranial angulation, lateral (90 degrees) RAO 45 degrees and RAO 110 degrees associated with 15 degrees of cranial angulation

The coronary angiograms were read separately by two observers. The hemodynamic measurements included left ventricular systolic and end diastolic pressures, aortic pressure, cardiac output, left ventricular stroke work, and peripheral arterial resistances. Tracings were made of end systolic and end-diastolic images of the left ventricle. The respective volumes were measured (Simpson s rule) using a computer system (Gra fomed Philips) which also allowed us to obtain quantitative and qualitative information on wall motion. Percentage of abnormally contracting segment (ASC) was determined with a map measurer by the length of wall involved and was expressed as the percentage of total end-diastolic perimeter Angiographically determined mean velocity of circumferential fiber shortening (mean $\overline{VCF}$) in circumferences/sec. was determined by the equation (π DED$-\pi$ DES)/π DED × ejection time, where π DED = end-diastolic circumference, π DES = end systolic circumference and ejection time was measured from the aortic curve recorded just before angiography however three VCF were determined from three specific minor diameters basal $\overline{VCF}$ middle $\overline{VCF}_m$ apical $\overline{VCF}_a$. Mean $\overline{VCF} = \overline{VCF} + \overline{VCF} + \overline{VCF}_a/3$.

The time from the onset of the infarction to the investigation averaged 16.1 ± 4.3 days for anterior infarct and 15.8 ± 3.3 days for posterior infarction (Fig. 1) Sixty-six per cent of the angiographic studies were performed between the fourteenth and twenty first day after the acute incident and

Table II Anterior infarction—functional significance of collateral circulation

	Cardiac index (L/min/M²)	*LVEDP (mm. Hg)*	*LVEDV (mL/M²)*	*% ACS (%)*	*EF (%)*	*VCF (circ/sec)*
Adequate collateral circulation (n = 8)	3.3 ± 0.34	14.7 ± 2.1	6 ± 8.1	31.5 ± 4.2	54.5 ± 3.5	0.96 ± 0.18
Inadequate collateral circulation (n = 12)	2.9 ± 0.28	19.7 ± 2.5	109 ± 10	47 ± 4	34.5 ± 4.8	0.80 ± 0.18
p	NS	NS	< 0.05	< 0.01	< 0.01	NS

LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume, % ACS = percentage of abnormally contracting segment, EF = ejection fraction; VCF = mean velocity of circumferential fiber shortening.

32 per cent were performed between the seventh and thirteenth day Informed consent was obtained from each patient.

Results

A. Risks involved Coronary arteriography can be performed without excessive risk following an acute coronary infarction In our series, one patient experienced a dyspnea attack after coronary arteriography which was easily reversed by an injection of furosemide. Two patients experienced benign inguinal hematomas which were related to anticoagulant treatment.

B *Coronary artery lesions.* In each group the main lesion responsible for the infarct, the collateral circulation, and the state of the other vessels were studied.

I Patients with an anterior infarction (n = 45). Table I shows the lesions in the left anterior descending artery (LAD) A lesion in this artery was shown by angiography in 44 out of 45 cases. Three subgroups can be distinguished

a. Twenty out of 45 patients (44 per cent) had *complete proximal obstruction of the left anterior* descending artery Seventeen of them had no flow beyond the obstruction In three patients the flow was extremely diminished.

b. Sixteen out of 45 patients (36 per cent) had severe narrowing (76 to 95 per cent) of the left anterior descending artery

c. In eight out of 45 patients (18 per cent) the degree of narrowing of the left anterior descending artery was only moderate (50 to 75 per cent) In seven of these eight patients there was a good distal runoff, and only in one case were minimal irregularities observed in the arterial lumen One patient had a normal left coronary artery (as well as the right coronary artery artery) This was a 30-year-old man who developed an anterior infarction while playing in a soccer match.

Q waves were present in Leads V to V and in

Table III Remaining coronary arteries in anterior infarction

	Right coronary artery	*Left circumflex artery*		*Obtuse marginal*
		Proximal portion	*Distal portion*	
Totally occluded	7%			2%
Narrowing 75-95%	11%		11%	7%
Narrowing 50-75%	27%	16%	4%	15%
Normal or irregularities	56%	69%	60%	69%

In some patients left circumflex artery was either absent or slender

Lead I and aV_L, and the creatinine kinase was 850 I.U Ventriculography showed a large anteroapical akinetic area and coronary angiography was normal except for a very slight irregularity in the left anterior descending artery

In 12 of 20 patients with complete obstruction of the LAD the collateral circulation was either absent or inadequate. Eight patients had an *adequate collateral circulation with* clear and rapid filling of the distal segment of the artery beyond the obstruction. These collateral vessels were derived in five patients from the contralateral arterial system (right coronary artery) and in three patients from the ipsilateral system (left circumflex and marginal arteries) This collateral circulation had some functional significance. Table II shows that patients with adequate collateral circulation had a significantly better ejection fraction than those with an inadequate collateral circulation. Left ventricular end-diastolic volume and percentage of abnormally contracting segment were smaller in patients with adequate collateral circulation. There was however no significant difference in cardiac index left ventricular end-diastolic pressure, and VCF Investigation of the remaining coronary arteries

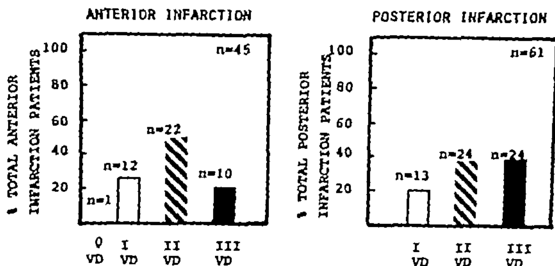


Fig. 2. Number of vessel disease in patients with recent myocardial infarction.

(Table III) showed that the right coronary was normal in 55 per cent of cases. But there was evidence of narrowing in 17 patients, and in three cases the right coronary artery was completely occluded. On the other hand total obstruction of the circumflex artery was very infrequent, and the different parts of the vessel (proximal, distal, and marginal circumflex) were normal in at least 60 per cent of the cases. Fig. 2 shows the distribution of these lesions. One vessel disease (LAD) was observed in 26 per cent (12 of 45) of patients. Forty nine per cent (22 of 45) had two vessel and 22 per cent (10 of 45) had triple vessel disease.

The pathology of vessels other than the left anterior descending artery was investigated in order to detect lesions amenable to an eventual aortocoronary bypass. Only severe proximal lesions with good retrograde filling and satisfactory ventricular function (ejection fraction above or equal to 30 per cent) could be considered for surgery. In accordance with these principles, four patients were considered for a single bypass of the right coronary artery, seven patients for a single bypass of the obtuse marginal artery and three patients for a double bypass of the right coronary and obtuse marginal arteries.

II Patients with a posterior infarction (n = 61). Lesions responsible for posterior infarction are more difficult to determine, but those of the right coronary artery (RCA) were responsible in 39 of 61 patients (64 per cent). In 11.5 per cent (7 of 61 patients) the infarction was the result of a lesion in only the circumflex artery. In 24.5 per cent (15 of 61 patients) the right coronary and circumflex arteries had similar lesions so that it was impossible to say which of the two was responsible for the infarction. As far as the most frequently affected vessel is concerned, namely the right coronary artery, it was shown that this artery was completely occluded in 36 of the 61 patients (59 per cent), considerably narrowed (75 to 95 per cent) in 18 percent, or slightly so in 11.5 per cent of cases. The distal runoff was absent in 36 of 61 patients. There was narrowing of the part distal to the lesion in three patients and in 15 this part appeared to be normal. There were two main areas of the right coronary in which lesions were found after a recent posterior infarction: just after the origin of the artery of the sinus node (22 per cent), and after the origin of the right ventricular branch (38 per cent). Eleven per cent of the lesions were very close to the origin of the RCA, 22 per cent of the principal lesions were close to the crux cordis, and 7 per cent were at the end of the vertical part of the RCA. An adequate collateral circulation was observed in 66 per cent (24 of 36) of patients who had complete obstruction of the right coronary artery (36 cases) or circumflex artery (one case). Normally the collateral circulation comes from a contralateral vessel, especially the LAD by way of the posterior descending artery but in 13 of the 24 cases the collateral contribution was generally slight.

The collateral circulation had, however, little influence on myocardial function, and Table IV shows that there was no significant difference in the cardiac index, left ventricular end-diastolic

Table IV Functional significance of collateral circulation in posterior infarction

	Cardiac index (L/min/M²)	LVEDP (mm Hg)	LVEDV (mL/M²)	% ACS (%)	EF (%)	VCF (circ/sec)
Adequate collateral circulation (n = [illegible]4)	3.3 ± 0.[illegible]	14.[illegible] ± 1.2	69 ± 7	[illegible].5 ± 2.5	[illegible]0 ± 3	0.59 ± 0.0[illegible]
Inadequate collateral circulation (n = 12)	3.2 ± 0.16	13 ± 1	9[illegible].5 ± 6.5	2[illegible] ± 4.1	49 ± 4.5	0.90 ± 0.14
p	NS	NS	NS	NS	NS	NS

Abbreviations LVEDP left ventricular end-diastolic pressure LVEDV left ventricular end-diastolic volume ACS percentage of abnormally contracting segments, EF = ejection fraction, $\overline{VCF}$ = Mean velocity of circumferential fiber shortening

Table V Remaining coronary arteries in inferior infarction

	Left anterior descending	Proximal portion of circumflex	Distal portion of circumflex	Obtuse marginal
Totally occluded	3%	20%	[illegible]%	4%
Narrowing 75-95%	20%	15%	[illegible]	1[illegible]%
Narrowing 50-[illegible]%	31%	11%	13%	13%
Normal	46%	36%	1%	48%

pressure left ventricular end-diastolic volume the size of the akinetic area, the ejection fraction nor the $\overline{VCF}$ Lesions of the left coronary artery were frequently present (Table V) after a posteri or infarction the most frequent of which were those involving the left anterior descending artery 33 of 61 patients had a lesion of this vessel. The artery was not usually completely occluded (only two patients) but 12 patients has severe narrowing (5 to 95 per cent) and in 19 the stenosis was between 50 and 5 per cent. The left anterior descending artery was normal or had only insignificant lesions in 46 per cent (28 of 61 patients) Lesions of the circumflex artery were very common the proximal was free from disease in 13 out of 61 patients and the marginal artery was normal in 48 per cent of cases. Fig 2 shows that only 21 per cent of patients suffering from a posterior infarction had a single lesion the number with two or three lesions were the same that is, 24 patients (39.5 per cent) Taking into account the character of the lesions, the quality of distal runoff and ventricular function (left ventricular end-diastolic pressure end-diastolic volume, ejection fraction, and $\overline{VCF}$) there were 31 patients (51 per cent) who could be considered for eventual aortocoronary bypass.

A single bypass could be proposed for 15 patients, generally on the left anterior descending artery A double bypass could be proposed for the 16 other patients, one on the left anterior descending artery and the other on the marginal artery

Discussion

Usually coronary angiography is not performed during the acute phase of myocardial infarction, but in practice the investigation is usually well tolerated and we have observed no serious complications. These results are in agreement with the findings of Begg and colleagues who performed without incident coronary arteriography on five patients 10 to 21 hours after the infarct and on 40 patients investigated during the third and fourth weeks after the onset of the infarction. No incidents or casualties are mentioned in the studies reported by Williams and co-workers or by Miller Our results show that the procedure can be undertaken without serious risk soon after an acute infarction and before the patient leaves the hospital. The results are of great importance with regard to five special problems (1) the aspect of the lesions responsible for infarct, (2) the collateral circulation, (3) the effect of age (4) complications and their relation to coronary artery lesions, and (5) lesions in the remaining coronary arteries.

1 **Lesions responsible for the acute myocardial infarction** There are numerous autopsy reports on the state of the coronary arteries in patients who have died from a coronary infarct, but the results vary according to whether or not a contrast medium was used to visualize the vessels. An examination of 10 pathological reports,[-] published from 1920 to 1974 comprising 1 143 cases, shows an incidence of 68.3 per cent of

Table VI Effects of occlusion or narrowing of the coronary artery responsible for the myocardial infarct on left ventricular function

	Anterior infarction		*Posterior infarction*	
	L.A.D totally occluded	*Narrowing of L.A.D*	*R.C.A totally occluded*	*Narrowing of R.C.A*
Cardiac index (L/min/M.)	3.1 ± 0.21	3.0 ± 0.15	3.3 ± 0.14	3.0 ± 0.23
LVEDP (mm. Hg)	17.5 ± 1.8	15.5 ± 1.3	13.3 ± 1	14.1 ± 1.6
LVEDV (ml./M.)	98 ± 8	91 ± 5.5	90 ± 5	74 ± 3.5
%ACS	41 ± 3.5	39 ± 2.7	28.5 ± 2.2	30 ± 2.4
EF (%)	43 ± 4	45 ± 2.8	49.5 ± 2.5	48 ± 2.5
$\overline{VCF}$ (circ./sec.)	0.75 ± 0.1	0.83 ± 0.07	0.96 ± 0.06	0.9 ± 0.06

Abbreviations: L.A.D = left anterior descending artery; R.C.A = right coronary artery; L.V.E.D.P = ventricular end-diastolic pressure; L.V.E.D.V = Left ventricular end-diastolic volume; % A.C.S = percentage of abnormally contracting segment; E.F = ejection fraction; $\overline{VCF}$ = Mean velocity of circumferential fiber shortening.
$p < 0.01$.

Table VII Frequency of total occlusion in recent and previous infarction

	Acute infarct study < 16 days	*Previous infarct*	
		Study before 1 year	*Study after 1 year*
Total occlusion	53%	56.5%	81%
Narrowing > 50%	47%	43.5%	19%

complete occlusion. On the other hand, when the injection of a contrast medium was used, incidence of complete occlusion was only 50.8 per cent. It was therefore of interest to know the incidence of complete obstructions in patients surviving an acute infarction. In our data, 53 per cent of cases had a complete occlusion which is considerably higher than those in the study of Begg[1] (77 per cent). Recently Oliva and Breckinridge[14] had clearly demonstrated that in the first 12 hours of acute myocardial infarction coronary arterial spasm was superimposed on a subtotal atherosclerotic obstruction and produced subsequent infarct. We have observed that 47 per cent of our patients had a stenosis of coronary artery of more than 50 per cent in the infarct region. Our observation seems to support the hypothesis by Oliva and Breckinridge[14] that the spasm can be initiating factor in the process of acute myocardial infarction. As Begg and co-workers noticed, the incidence of single lesions responsible for the infarction was higher in the anterior (56 per cent) than in posterior infarction (41 per cent). The objection could be made that the injection of contrast medium into vessels during coronary angiography is artificial in that the pressure required to inject is higher than that of the normal coronary circulation. It might therefore be thought that the pressure required for injection might overcome the obstacle and inject the vascular bed. However in two patients suffering from an anteroseptal infarction coronary angiography was performed at 15 and 30 days respectively before the infarction, and these two patients had a 75 per cent narrowing of the anterior descending artery which had changed little when reexamined 18 and 21 days after the onset of the infarct. It is, however, clear that narrowing or complete obstruction of the vessel responsible for the infarction have the same effect on ventricular function (Table VI) as there was no significant difference in the cardiac index, left ventricular end-diastolic pressure, left ventricular end-diastolic volume, the size of the akinetic area, the ejection fraction, nor the $\overline{VCF}$. It should, however be noted that patients with a posterior infarct have a smaller end-diastolic volume ($P < 0.01$) when the right coronary system is narrowed (LVEDV = 74 ± 3.5 ml./M.) than when the vessel is completely occluded (LVEDV = 90 ± 5 ml./M.). When the respective incidence of complete occlusions and narrowing of the vessels are considered in relation to the time after the onset of the infarction, it can be shown that in 105 patients (one had normal coronary arteries) the percentage of occlusion and stenosis was the same in patients investigated

Table VIII Effects of age on lesions and collateral circulation

Lesions	*None*	*One vessel disease*	*Two vessel disease*	*Three vessel disease*
Below 45 yrs. old	4%	27%	36%	33%
Above 45 yrs. old		26%	47%	27%
χ^2 = 1.19 (NS)				
Collateral circulation		*Absent*	*Slight*	*Moderate*
Below 45 yrs. old		43%	28.5%	28.5%
Above 45 yrs. old		54.8%	28.6%	16.6%
χ^2 = 1.32 (NS)				

Table IX Complications and their relation to coronary artery lesions

	One vessel disease	*Two vessel disease*	*Three vessel disease*
Posterior infarction			
Complete A V block (= 12)	3	7	2
Ventricular fibrillation (= 7)		4	3
Uncomplicated (n = 34)	8	12	14
Anterior infarction			
Complete A-V block (= 2)		2	
Ventricular fibrillation (= 5)	1	3	1
Uncomplicated (= 37*)	11	17	9

*One patient had no vessel disease.

either during the second or third week. It is interesting to compare the percentage of complete occlusion in another group of 72 patients (30 anterior and 42 posterior infarcts) investigated at a later date. Table VII shows that 56.5 per cent of those investigated within a year (2 to 12 months after the infarct) had one occlusion, which is comparable with the findings during the acute phase. However coronary angiography carried out 12 to 24 months after the infarct showed 81 per cent of complete occlusion while the percentage of stenotic lesions had fallen to 18.6 per cent, compared with 47 per cent during the acute phase. This suggests that in some patients the lesion which was initially responsible for the necrosis had progressed to produce a later complete occlusion. We have been able to repeat a second coronary angiography at an average time of 24 months after the first examination, in six patients, three had anterior and three had posterior infarctions. Among those with a posterior infarction, the completely obstructed right coronary artery had become revascularized in two cases, and one patient remained unchanged. Among the three cases with an anterior infarction, there were two with a complete occlusion and these remained unchanged the third case had a stenosis which did not appear to be appreciably different from that seen at the first examination.

2 The collateral circulation In evaluating the collateral circulation we have only accepted those patients with complete occlusion of the vessel responsible for the infarct. A collateral circulation was judged to be present only when the vessel beyond the obstruction could be visualized. In the case of the right coronary artery we have accepted those cases where the region of the right coronary artery close to the crux cordis has been visualized for the anterior descending artery opacification of the part distal to the obstruction was required.

With these criteria 32 of our 57 patients (56 per cent) had a collateral circulation supplying the infarct area. This collateral circulation was generally slight at this time after the infarction but it probably develops later Hamby and associates have shown that 79 per cent of 465 patients with a complete obstruction of the left anterior descending artery had collateral vessels. In our series a collateral circulation was more common with a posterior infarct and obstruction of the right coronary artery (65 per cent), than with anterior infarction and obstruction of the left anterior descending artery (40 per cent) It is difficult to evaluate the functional value of the collateral circulation, because coronary angiography gives no quantitative information on the blood flow in these vessels. It is, however possible to estimate the influence of the collateral circulation on myocardial function. The results show that the collateral circulation had a protective effect in cases of anterior infarction with complete obstruction of the left anterior descending artery as these patient had a significantly higher ejection fraction a smaller left ventricular end diastolic volume, and the percentage of abnormally contracting segment was less th

patients without a collateral circulation (Table II)

Our results are in keeping with those of Hamby and colleagues. In common with these authors we have not detected a protective effect from the collateral circulation in patients with a posterior infarction and total obstruction of the right coronary artery (Table IV) The absence of a protective role of the collateral vessels in patients with obstruction of the right coronary artery may be a matter of methodology as angiography in a single plane shows the posterolateral wall of the left ventricle rather poorly

3 **The effect of age** Patients can be divided into two groups those below and those above 45 years of age. Table VIII shows the number of lesions and the size of the collateral circulation in each group. Although there were slight differences between the two groups, it appears that age has no effect on the distribution and number of lesions nor on the development of a collateral circulation

4 **Complications and their relation to coronary artery lesions.** Nineteen patients with a posterior infarction presented with complications. These were mostly arrhythmias—complete A V block in 12 cases and ventricular fibrillation in seven cases. Characteristics of the lesions in these patients were compared with those of a group of 34 patients with posterior infarctions who had no complications. Table IX shows that the incidence of a single lesion is the same in those who had A V block and in those who had no complications. Double vessel disease were rather more frequent in the A V block groups, but triple lesions were common in the uncomplicated group Ventricular fibrillation however was most often seen in patients suffering from an infarct, either anterior or posterior associated with two or three vessel disease. In general, it seems that no distinction can be made on the basis of the location and severity of the lesions between those who had complications and those who did not

5 **Lesions in the remaining coronary arteries** These were very common. Most often, more than one vessel was involved 43 per cent of patients had lesions in two vessels and 32 per cent had lesions in three vessels. The major problem concerns the group of patients with posterior infarction and significant lesions in two or three vessels, because this group shows a relatively high annual mortality rate.

Accordingly the prognosis could possibly lie with the degree of patency of the left anterior descending artery If there is a significant proximal narrowing of this artery in patients with posterior infarction it puts them in a high risk category

Various studies have shown that longevity in patients with chronic coronary artery disease is related to the number of major coronary vessels that are stenotic. With this in mind as was recently demonstrated by Miller and colleagues, it appears logical to define the coronary pathology with angiography to provide a more accurate prognosis.

We conclude

1 That 47 per cent of patients studied in the early post-myocardial infarction period had only a stenosis of the coronary artery responsible for the infarct, and this observation supports the hypothesis of Oliva and Breckinridge that spasm could be an initiating factor in the processus of infarction.

2 Collateral circulation had a protective effect only in patients with anterior infarction

3 The age has no effect on the coronary arterial patterns associated with acute myocardial infarction.

4 Candidates for saphenous vein bypass grafting were identified in 31 of 61 patients with posterior infarction and in 14 of 45 patients with anterior infarction.

Summary

Coronary arteriography was performed 16 ± 3 days (range 7 to 21 days) in 106 patients with acute transmural myocardial infarction (61 posterior infarct, 45 anterior infarct) Coronary arteriography was performed without serious complications. Only 44 per cent of patients with anterior infarct had total occlusion of the left anterior descending artery while a significant stenosis of the vessel was observed in the others —27 per cent had a single vessel disease, 49 per cent had two lesions and 22 per cent had three lesions, one patient had angiographically normal coronary arteries. Among the patients with posterior infarction, 21 per cent had one vessel disease and double or triple lesions accounted for 39 per cent of each

Sixty per cent of patients with anterior infarction and 45 per cent with posterior infarction had no collateral vessels. In the others patients collat

eral circulation had a protective effect only in anterior infarction. Age has no effect on the distribution and number of lesions nor on the development of a collateral circulation. The location and severity of the lesions were not different in patients who presented with arrythmias and those who did not.

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Coronary collaterals in the canine heart development and functional significance

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The development of coronary collaterals after progressive coronary artery obstruction has been intensively studied in the dog heart. In general, indirect indices such as retrograde flow and peripheral coronary pressure were used to assess the degree of collateralization. However a quantitative determination of coronary collateral resistance and its changes during different stages of collateral development was not attempted because of the lack of adequate methods for the measurement of regional blood flow. Some authors tried to measure collateral flow directly with radioactive tracers such as Rubidium-86 Xenon-133, and Krypton-85 but these tracers produced conflicting results. A recent development has been the determination of the distribution of regional flow with tracer microscpheres. With this technique, regional coronary flow and coronary collateral flow could be determined within a fair range of accuracy.

In this study we used the tracer microsphere technique to investigate (1) the changes in collateral resistance after chronic coronary occlusion and (2) the functional capacity of these collaterals under conditions of cardiac stress.

Methods

The experiments were carried out in 18 mongrel dogs with an average body weight of 21 Kilograms.

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Design of the experiments.

A Group I (8 dogs)

1 CONTROL STUDY Determination of the resistance of preexisting collaterals during short transient coronary occlusion thereafter implantation of an Ameroid constrictor to occlude the coronary artery slowly during the next 2 to 3 weeks.

2. FINAL EXPERIMENT Six weeks after the control study reevaluation of the collateral resistance after chronic coronary occlusion aortocoronary bypass grafting and study of the regional coronary reserve with open and closed graft. *Pathology* Frequency of myocardial infarction after chronic coronary occlusion.

B Group II (10 dogs).

1 Implantation of an Ameroid constrictor no control study

2. FINAL EXPERIMENTS. Six week after constrictor implantation, stress test to evaluate the functional capacity of developed collaterals connection of an aortocoronary bypass and study of regional myocardial blood flow during norepinephrine infusion with open and closed graft.

Experimental procedures

A Group I

1 CONTROL STUDY Eight animals were operated upon under sterile conditions during anesthesia with piritramide (2.5 mg./Kg. subcutaneously) and sodium pentobarbital (15 mg./Kg. intravenously) For artificial respiration a Bird Mark 7 respirator was used. A thoracotomy was performed through the fourth left intercostal space and the heart was suspended in a pericardial cradle The circumflex branch of the left coronary artery (LC) was dissected free close to its origin. Arterial pressure was measured with a

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Bell & Howell pressure transducer via a catheter placed in the ascending aorta and in the left circumflex coronary artery. During short occlusion of the LC, tracer microspheres (TM) were injected into the left atrium. ECG Lead II, aortic pressure, and peripheral coronary pressure (PCP) were registered on a Siemens ink jet recorder. The TM distribution was calibrated with the reference-sample method *(see below)*. In four dogs the acute LC occlusion was performed during infusion of dipyridamole (0.5 mg./Kg.). After release of the LC occlusion an Ameroid constrictor was implanted at the site of the previous LC occlusion. The chest was closed and the dogs were allowed to recover.

2. FINAL EXPERIMENT. Six weeks later the animals were rethoracotomized. The anesthesia was maintained with 60 + 20 nitrous oxide oxygen using a Bird Mark 7 Mark 5 combination. To ensure complete closure of the constrictor, the LC was ligated directly distal to the constrictor. Aortic and peripheral coronary pressure (PCP) were measured. All variables including ECG Lead II were recorded. During infusion of dipyridamole (0.5 mg./Kg.), tracer microspheres were injected into the left atrium and blood was withdrawn from the femoral artery for calibration of the microspheres *(see TM section)*. Thereafter the saphenous vein was grafted between the descending aorta and the LC distal from the constrictor. Again dipyridamole was infused. TM were injected when the graft flow measured with an electromagnetic flowmeter stabilized at a high level. In four dogs an additional TM injection was made directly into the graft. Next the animals were killed with an overdose of pentobarbital and the heart was removed.

B. Group II. In 10 dogs, an Ameroid constrictor was implanted on the LC as described above. Six weeks later final experiments were performed using the same anesthesia as in Group I. Because of the difficult procedure of vein grafting in the beating heart, a silicon rubber shunt was used in this group of dogs to produce aortocoronary bypass. After rethoracotomy, the LC was ligated directly distal from the constrictor and a slightly bent metal cannula connected to a silicon tubing was inserted into the LC distal from the Ameroid constrictor. The proximal part of the tube was connected to another bent metal cannula which was then inserted into the left subclavian artery. Both cannulas and the silicon rubber tubing had

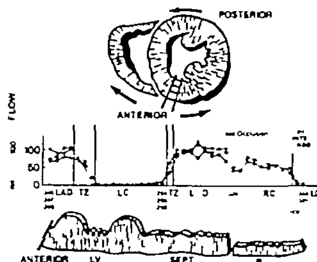


Fig. 1. Mapping of regional myocardial blood flow. The heart is sliced perpendicular to the apex–base axis and the left ventricle is separated from the right. The slices are unrolled and divided into sections (counterclockwise for the left ventricle and clockwise for the right ventricle). Each section is further divided into subepicardial, intermediate, and subendocardial tissue sample. Sections from the right ventricle are divided into subepicardial and subendocardial sample only. When local flows are plotted against their sample number, regional flow "mapping" is obtained. This is shown in this figure. TM were injected during acute occlusion of the left circumflex coronary artery. The area between lines represents the transitional zone, perfused by both LAD and the LC.

an inner diameter of 3 mm. After connection of the shunt, the same hemodynamics as in Group I were measured. In five dogs TM were injected into the left atrium with closed and open shunt. Then norepinephrine 2 μg/minute/Kg. was infused in all animals after cutting both nervi vagi and an injection of TM was performed with open and closed shunt. Finally the animals were killed and the hearts removed.

TRACER MICROSPHERES. Regional myocardial blood flow was measured with the TM technique. Six different isotopes were used: I 125, Ce-141, Cr-51, Sr-85, Nb-95, and Sc-46. The Nb and I-spheres had a diameter of 15 μ, the others were 8 to 10 μ.

After the experiment, the heart was removed and fixed in phosphate-buffered 4 per cent formaldehyde for two days. The atrial cap was removed and the ventricles were sliced perpendicular to the apex–base axis with a calibrated sausage slicer. As presented in Fig. 1, each slice was unrolled and the left ventricle was isolated from the right. The unrolled slice was divided into tissue sections counterclockwise from the free

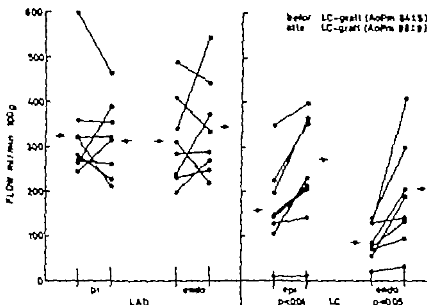


Fig. 2. Regional coronary reserve after chronic coronary occlusion and the effect of surgical revascularisation. (Group I animals). Maximum coronary flow values before *LC* grafting are presented by *closed circles* and by *open circles* after LC grafting. *LAD* = perfusion area of the left anterior descending coronary artery; *epi* = subepicardium, *endo* = subendocardium, *LC* = perfusion area of the chronically occluded left circumflex coronary artery. *AoPm* = mean aortic pressure ± standard error; Θ = mean flow values. The p values indicate that mean flow values before and after LC grafting are significantly different. *ns* = not statistically significant (p > 0.05) = infarcted areas

Table 1 Development of coronary collaterals after chronic coronary artery occlusion (Group I animals)

	Pre-existing collaterals		*Developed collaterals*		
Dog No.	*Collateral resistance‡ (R U.)*	*Peripheral coronary pressure (%)‡*	*Collateral resistance (R.U.)†*	*Peripheral coronary pressure (%)‡*	*Pathology*
1	2.03	9	0.27	57	No MI‡
2	9.50	13	0.31	62	No MI
3	9.80	9	0.19	48	No MI
4	5.17	14	0.39	50	No MI
5	7.33	8	0.17	68	No MI
6	3.70	10	0.22	33	Subendo MI
7	6.40	11	0.36	47	Small transmural MI
8	27.00	10	2.19	23	Large transmural MI
m (±SE)‡	8.49 ± 2.77	10.5 ± 0.7	0.51 ± 0.24 p < 0.05§	49.9 ± 5.4 p < 0.001§	

*The collateral resistance of the preexisting collaterals was determined during short transient coronary occlusion at the time of constrictor implantation.

†The resistance of the developed collaterals was estimated six weeks after constrictor implantation, i.e., during chronic coronary occlusion.

‡Symbols and abbreviations: R U = resistance units (mm Hg/ml)/minute per 100 g); peripheral coronary pressure is expressed in per cent (diastolic PCP/diastolic aortic pressure times 100); MI = myocardial infarction; m = mean value ± standard error (SE)

§Values are significantly different from the corresponding values in the left panel.

wall of the left ventricle, over the posterior free wall to the interventricular septum, and clockwise from anterior to posterior for the right ventricle. Each section was further divided into an epicardial, endomural, and endocardial sample. The samples had an average weight of 400 mg.

Details concerning the measurement of radioactivity and data processing are described elsewhere. The TM data (c.p.m. ... u ... o cal-

brated to mL/minute/100 g by the reference sample method. For this purpose a wide-bore catheter was placed into the terminal aorta via the femoral artery and connected to a Gilford constant-speed withdrawal pump at 22 mL/minute.

Fig. 1 *(lower panel)* shows such a mapping of myocardial flow distribution during acute occlusion of the LC. The horizontal axis represents the anatomical localization of the samples on the unrolled slice.

Statistical significance of the data was analyzed using the Student t test.

Results

A. Group I

1. Collateral development. Collateral resistance was calculated as follows.

$$AoP - PCP / Coll. flow$$

where *AoP* = diastolic aortic pressure, *PCP* = diastolic peripheral coronary pressure, and *Coll.flow* = collateral flow to the LC area. Collateral resistance was expressed as resistance units (R.U.) mm. Hg/(mL/minute) per 100 g.

Mean resistance of the pre-existing collaterals was 8.49 ± 2.77 R.U. (see Table I). Note that the dog which developed a large myocardial infarction after chronic occlusion had the highest value of preexisting collateral resistance (27 R.U.).

After chronic LC occlusion, 6 weeks after implantation of the constrictor, collateral resistance decreased significantly ($p < 0.05$) to 0.51 ± 0.24 R.U. for the group as a whole. Again the highest collateral resistance was found in the dog with a large transmural infarction (see Table I). Peripheral coronary pressure increases significantly ($p < 0.01$) to five times control after chronic occlusion (see Table I).

2. Pathology. Five dogs of this group developed no myocardial infarction after chronic LC occlusion. One dog had a subendocardial infarction and the other two dogs developed a transmural infarction.

3. Regional coronary reserve after chronic coronary occlusion and the effect of surgical revascularisation. Regional myocardial blood flow distribution during maximum vasodilation (dipyridamole) in dogs with chronic LC occlusion is shown in Fig. 2. In the normal perfused LAD area *(left panel)* flow increases to an average of 332 mL/minute/100 g for the subepicardium and 313 mL/minute/100 g for the subendocardium after chronic LC occlusion *(closed circles)*. Aorto-

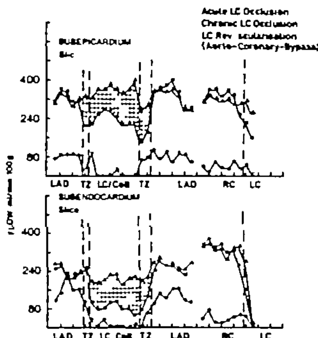


Fig. 2. Myocardial blood flow distribution in the third slice of heart without myocardial infarction. TM ere injected during acute occlusion of the left circumflex coronary artery, six weeks later after chronic occlusion of this vessel, and after aortocoronary bypass grafting. Regional flow during chronic occlusion and after revascularisation as measured during maximum coronary vasodilatation. *Upper panel* = subepicardial flow (ml./minute/100 g). *Lower panel* = subendocardial flow (mL/minut /100 g). *LAD* = perfusion area of the left anterior descending artery. *LC* = perfusion area of the left circumflex. *RC* = perfusion area of the right coronary artery. *TZ* = transitional zone.

coronary bypass on the LC *(open circles)* had no significant influence on the flow to the LAD area ($p > 0.05$). In the collateral dependent area *(right panel)* the subepicardium receives 160 mL flow/minute/100 g and the subendocardium 88 mL/minute/100 g *(closed circles)*. These flows are significantly lower than the corresponding values in the LAD area ($p < 0.01$). Bypass grafting does not restore coronary reserve completely in the LC region *(open circles)*. Flow to the subepicardium increases significantly ($p < 0.01$) to 274 mL/minute/100 g after bypass and flow to the subendocardium is also significantly augmented ($p < 0.05$) to 187 mL/minute/100 g. LC-epi flow after bypass is not significantly different from LAD-epi flow ($p > 0.05$) but LC-endo flow after bypass is significantly lower than LAD-endo flow ($p < 0.05$). This incomplete restoration of coronary reserve, however should be seen in the light of the pathology in the involved area. In the animals with macroscopic signs of previou infarctions, regional coronary reserve

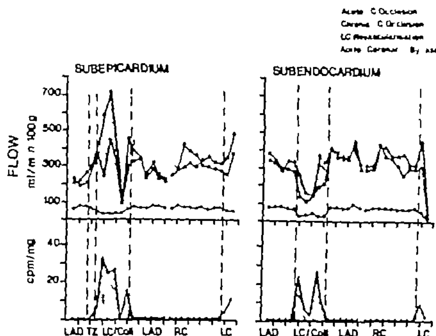


Fig. 4. Myocardial blood flow distribution during maximum vasodilatation in a heart with subendocardial infarction. The subepicardium *(left panel)* has an almost normal dilatory reserve after chronic LC occlusion, except for one sample which was infarcted. Injection of TM directly into the bypass *(lower panel)* shows that the entire subepicardium can be reperfused with exception of the infarcted sample. The center of the subendocardial layer *(right panel)* is infarcted and cannot be reperfused. This is also demonstrated when TM are injected into the bypass only *(lower panel)*. The same abbreviations were used as in *Fig. 3*.

severely impaired in the infarcted layer after bypass (see Fig. 2) In the animals without infarctions, maximum flow increased to nearly normal values. Mean aortic pressure did not change significantly ($p > 0.05$) after bypass grafting. Average minimum resistance (mean aortic pressure/local flow) was 0.24 R U ± 0.02 (SEM) in the LAD subepi and subendocardium

To study regional flow more detailed "mappings" of myocardial blood flow were made. Fig. 3 represents such mapping in one of the hearts without infarction In the tissue samples of the transitional zone (TZ) it is impossible to tell anything about collateral flow because they have a mixed supply from both the LAD and the LC (see also Fig. 1) Flow over the preexisting collaterals during acute LC occlusion *(circles)* was at a constant level in all tissue samples of the LC area. This collateral flow increased significantly after chronic occlusion *(rectangles)* but was still less than the flow to the LAD After bypass grafting regional flow reserve was again homogenous *(triangles)* *Fig. 4* shows the myocardial blood flow distribution in Dog 6 with macroscopic signs of subendocardial infarction Although the collateral flow increased remarkably the subendocardium could not be reperfused completely This is also shown in the lower panel when TM were injected into the bypass, almost no radioactivity was detected in the center of the LC perfusion area. One tissue sample of the subepicardium could also not be reperfused *(left panel)*. Figs. 5 and 6 represent the distribution of flow in Dogs 7 and 8, which developed a transmural infarction after chronic LC occlusion. The center of the LC area was poorly perfused after chronic occlusion but collateral flow increased significantly in the more peripheral zones of this region Microscopic studies of these hearts showed severe fibrosis in the samples corresponding to the center of the infarction In the peripheral zone i.e., in those samples with a relatively high collateral flow a mixture of normal myocardium and fibrotic tissue was found. Only this border zone could be reperfused partially

B Group II None of the animals in Group II had macroscopic signs of a myocardial infarction after chronic LC occlusion. Pressure-rate product (mean aortic pressure times heart rate = PRP) was calculated at rest and after infusion of norepinephrine with open and closed LC shunt. The relationship between regional blood flow and PRP is presented in Fig. 7 With closed shunt

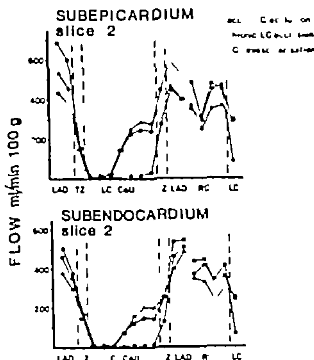


Fig. 5. Myocardial blood flow distribution during maximum vasodilatation in the heart with small transmural infarction after chronic LC occlusion. The area of low flow during acute LC occlusion represents the perfusion area of this vessel. The infarction after chronic LC occlusion is about half of the perfusion area. The not infarcted borderzone can partially be reperfused. *Upper panel* = subepicardial flow. *Lower panel* = subendocardial flow. The same abbreviations were used as in *Fig. 3*.

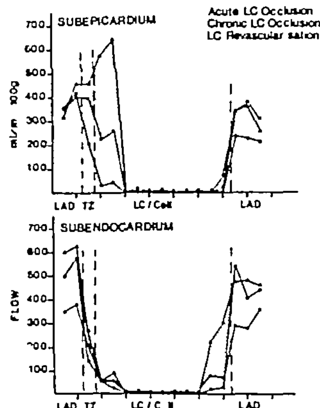


Fig. 6. Myocardial blood flow distribution during maximum vasodilatation in the heart with large transmural infarction. Almost the entire perfusion area of the LC is infarcted. Only the small border zone can be reperfused. *Upper panel* = subepicardial flow. *Lower panel* = subendocardial flow. The same abbreviations were used as in *Fig. 3*.

(closed circles, upper panel) myocardial blood flow to the LAD area increases linearly with PRP ($p < 0.01$ for the subendocardium and $p < 0.05$ for the subepicardium). In the collateral dependent LC area, however *(middle panel)* there is no further increase in subendocardial flow with augmenting PRP ($p < 0.05$). Subepicardial collateral flow increases only slightly ($p < 0.01$) with rising PRP. This indicates that the collateral dependent areas are selectively underperfused under stress conditions. With open LC shunt the LAD flow *(open circles, upper panel)* remained unchanged. The PRP flow relation was significant as well for the subendo- ($p < 0.01$) as for the subepicardium ($p < 0.05$). With open LC shunt the linear relation between myocardial flow to the LC area and PRP *(lower panels)* is completely restored.

Discussion

Our results show that collateral resistance decreases remarkably during slow progressive coronary artery stenosis until complete occlusion. This direct and quantitative estimation of collateral resistance was never done before in the chronic experimental animal. In a recent study we determined collateral resistance with tracer microspheres in the isolated, empty beating dog heart. During collateral enlargement collateral resistance fell from 3.59 R.U. to 0.22 R.U. within a period of 8 weeks after implantation of the constricting device. These values are somewhat lower than those found in the present study. This can be due to the fact that in the previous study only hearts without myocardial infarctions were considered. Furthermore, the time after constrictor implantation was longer and also the difference in the experimental conditions may play some role.

Since only the anatomical determinants of resistance to flow were of interest, the experiments designed to measure collateral resistance had to be carried out at maximal coronary vasodilation. Because coronary flow during maximum

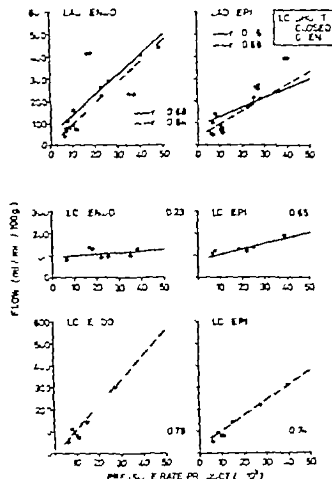


Fig. 7 Functional significance of coronary collaterals (Group II animals). Pressure-rate-product as an index of myocardial oxygen consumption was increased by norepinephrine infusion. *LAD-ENDO* = subendocardium perfused by left anterior descending artery. *LAD-EPI* = subepicardium perfused by the left anterior descending artery. *LC-ENDO* = subendocardium perfused by collaterals or by the LC-shunt, *LC EPI* = subepicardium perfused by collaterals or by the LC-shunt. *The straight lines represent the linear regression for data points with closed shunt and the dotted lines for data points with open shunt.* = correlation coefficient.

vasodilatation is linearly related to perfusion pressure the considerable variation of systemic arterial blood pressure between different animals is responsible for the wide scatter of flow data presented in Fig. 2. Minimum coronary resistance, however measured in areas perfused by normal coronary arteries was relatively constant 0.24 R.U ± 0.02 (SEM). This value is also slightly higher than that found in the isolated empty beating heart.

The fact that only three 18 animals developed a myocardial infarction provides strong evidence for the protective function of the collateral circulation against myocardial damage. Why these three dogs developed their myocardial infarction is difficult to tell and we do not have enough data to reach conclusions on the cause of these infarctions. Collateral flow is certainly not the only determinant of ischemia tolerance of the myocardium. Nevertheless, the high spatial resolution of the microsphere technique provides some interesting information about the regional perfusion in hearts with myocardial infarctions, in spite of the small number of cases. Although acute collateral flow seems to be homogenously distributed over the entire perfusion area of the LC only the center of this region becomes infarcted after chronic occlusion. Collateral flow increases, apparently at the border zones, and only these areas can be partially reperfused after bypass. In animals without myocardial infarction, collaterals are well developed, but their functional capacity is rather limited. When myocardial oxygen consumption is increased during infusion of norepinephrine coronary reserve in the collateral dependent areas becomes inadequate. The collateral dependent area cannot raise its blood flow to levels which are observed in the myocardium supplied by normal coronary arteries and this results in regional ischemia.

Clinical implications. A critical point concerning the clinical implications of our study is that there is no data to suggest that collaterals in man are comparable to collaterals in the dog heart. With this restriction, the data contained in this study seem to document what Blumgart and associates suggested in 1940 i.e., that patients with complete coronary artery obstruction and collateral vessels were able to maintain resting requirements *of the heart but not the demands of* increased work load. These findings are also in agreement with the failure of many investigators to observe any effect of collaterals on physical work capacity or response to exercise stress. Thus significant collateral circulation might protect the myocardium against infarction in most cases, but blood flow becomes inadequate under stress conditions.

Summary

The development and functional significance of coronary collaterals was studied using the tracer microspheres technique in 18 mongrel dogs with complete chronic occlusion of the left circumflex coronary artery

In a first group of eight dogs resistance of the

preexisting collaterals was determined during short acute occlusion of the left circumflex coronary artery (LC). The mean value was 8.49 resistance units (R.U.). Six weeks after the implantation of an Ameroid constrictor on the LC, collateral resistance decreased significantly ($p < 0.05$) to 0.51 R.U. Only two dogs of this group developed a transmural infarction and one a subendocardial infarction after chronic LC occlusion. Aortocoronary bypass grafting restored regional coronary reserve completely in dogs without infarction and partially in dogs with infarction.

In the second group of 10 animals no myocardial infarction was found six weeks after Ameroid constrictor implantation. In this group a stress test was performed by infusion of norepinephrine intravenously.

In the areas perfused by normal coronary arteries, there was a significant relation between myocardial blood flow (MBF) and pressure-rate product (PRP). The collateralized subendocardium, however, failed to raise its blood flow with increasing PRP. After bypass to the occluded LC the normal MPF-PRP relation was restored.

These observations indicate that a significant collateral circulation develops after chronic coronary obstruction and protects the myocardium against infarction in most cases. The functional capacity of these collaterals, however, is limited and becomes inadequate under stress conditions.

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Comparative effect of counterpulsation and bypass on left ventricular myocardial oxygen consumption and dynamics before and after coronary occlusion

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Circulatory assistance is considered useful in the treatment of cardiogenic shock, refractory left ventricular failure, unstable angina pectoris, and postoperative myocardial depression following coronary artery bypass surgery. The goal of circulatory assistance is a decrease in left ventricular workload with resulting decrease in myocardial oxygen consumption (MVO_2).

Intra-aortic balloon counterpulsation decreases left ventricular workload by reducing afterload and improves the transmyocardial perfusion gradient and myocardial oxygen delivery by augmenting the arterial diastolic and decreasing the left ventricular diastolic pressures. In contrast to counterpulsation, left ventricular bypass is thought to decrease left ventricular workload by decreasing preload. Since preload is a lesser determinant of MVO_2 in comparison to afterload, it has been suggested that left ventricular bypass must be complete in order to substantially decrease MVO_2. This appears to be particularly true in preparations with fixed stroke volume and thus no major changes in diastolic wall tension.

During both counterpulsation and left ventricular bypass, changes in systemic resistance may occur and thereby alter MVO_2. In previous studies comparing reduction of MVO_2 by these two methods, systemic resistance was not adequately controlled. The object of this study was to evaluate and compare the effects of balloon counterpulsation and left ventricular bypass on left ventricular MVO_2 and function before and after coronary artery occlusion in a canine preparation with rigidly controlled heart rate, cardiac output, and mean arterial pressure.

Methods

Twenty mongrel dogs weighing 25 to 30 kilograms were anesthetized with intravenous pentobarbital sodium (30 mg./Kg. of body weight). Following intubation with a cuffed endotracheal tube, the animals were ventilated using a volume respirator (Harvard Apparatus Co., Dover, Mass.) and a mixture of 97 per cent oxygen and 3 per cent carbon dioxide. Arterial pressure was monitored from the beginning of the study via a No. 8 Cournand catheter introduced into the right carotid artery and connected to a Statham (Hato Rey, Puerto Rico) P23Db pressure transducer. The heart was exposed through a midline sternotomy and the azygous vein and venae cavae were prepared for right heart bypass. The pericardium was opened using a longitudinal incision, the

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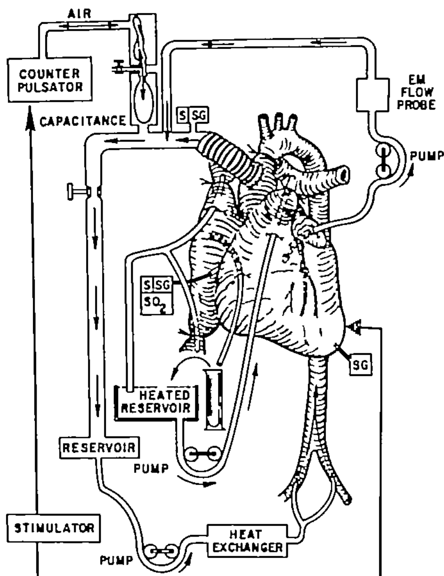


Fig. 1 Diagram of experimental preparation. S = sample, SG = strain gauge.

periaortic fat was excised, and umbilical tapes were placed around the pulmonary artery and ascending aorta.

In all animals left ventricular workload and heart rate were uniformly controlled as described in detail elsewhere[1] (Fig. 1) In brief, the heart rate was fixed at 120 min. by means of ventricular pacing following induction of complete atrioventricular block. Cardiac output was maintained at 120 ml min Kg. BW using the right heart bypass technique. Mean aortic pressure was kept constant at 70 mm. Hg by diverting the left ventricular output, minus coronary flow to an extracorporeal circuit with adjustable resistance and capacitance, through a Dacron graft sewn on the ascending aorta, then ligating the aorta between the graft and the origin of the brachiocephalic trunk. Capacitance adjustment was used to maintain aortic end-diastolic pressure above 55 mm. Hg and systolic above 120 mm. Hg as monitored via a side tube of the circuit. All extracorporeal circuits were primed and supplemented with fresh heparinized donor blood and saline so that during the study the hematocrit was maintained between 35 and 45 per cent.

The blood, warmed by a heat exchanger was returned to the animal via cannulas in both femoral arteries using a second occlusive roller pump. Proximal aortic root pressure was monitored via a side tube of the circuit distal to the

aortic graft, using another pressure transducer. Left ventricular pressure and its first derivative, left ventricular dp/dt, were measured with a catheter tip pressure transducer (Millar Instruments, Houston, Texas) introduced into the left ventricle via its apex.

The tip of a double lumen fiberoptic catheter (Edwards Laboratories, Santa Ana, Calif.) was placed in the coronary sinus via the right atrial appendage and connected to a pressure transducer and an In Vivo oximeter (Physio Control, Seattle, Wash.) for pressure and oxygen saturation monitoring. The mean and phasic aortic pressure, the left ventricular pressure, the mean coronary sinus pressure, the body surface electrocardiogram, the left ventricular dp/dt, and the coronary sinus saturation were continuously recorded using an oscillographic recorder (Honeywell 1612, Denver, Colo.)

The temperature of the animals was maintained at 36.5 to 37 degrees Celsius by adjusting the reservoir heater setting and heat exchanger water flow as measured in the venous outflow using a digital thermometer (Bailey Instruments, Saddle Brook, N. J.).

Total coronary blood flow excluding left Thebesian drainage, was determined by repetitive (five to 10) timed collections (30 to 60 seconds) of the continuous siphon drainage of the right heart chambers.

Blood samples were obtained from the arterial circuit and the coronary venous outflow and were iced immediately after collection for later determination of oxygen content by the Van Slyke method. Using the Astrup apparatus the pH, pO_2 and pCO_2 of blood samples were determined along with the hematocrit. Myocardial oxygen consumption was derived as the product of coronary blood flow and the corresponding arteriovenous difference, and was then indexed to 100 Gm. of left ventricular myocardium *(vide supra)*. In this preparation total myocardial oxygen consumption derived as described, closely approximated left ventricular myocardial oxygen consumption.

Pericoronary snare placement for later coronary ligation was performed in seven of the animals using blunt dissection and cotton covered instruments. The snare was placed in all animals around the anterior interventricular branch of the left coronary artery (left anterior descending) just distal to the origin of the first diagonal branch.

Data were collected at steady state conditions during control period, during counterpulsation, and during varying degrees of left ventricular bypass both before and after coronary ligation.

Maximal balloon counterpulsation was accomplished in the following manner: a second rigid chamber containing another balloon was connected to the capacitance apparatus of the systemic circuit so that the two balloons were connected with a short tube (Fig. 1). Air volume equal to the animal's fixed stroke volume (1 ml/kg. BW) was introduced into the second balloon. During counterpulsation the second balloon collapsed, further inflating the first balloon by a volume equal to the stroke volume. The synchronization signal for the compressed air operated counterpulsation device* was obtained from the electrical stimulator driving the ventricle. Proper setting of the electronic delay and duration assured the occurrence of counterpulsation wave during diastole, as tested by high paper speed (100 mm./sec.) pressure recordings.

Left ventricular bypass was accomplished by introducing a No. 36 Bardic cannula into the left atrium via the left atrial appendage, through which blood flow could be diverted from the left atrium to the systemic bypass circuit using a roller pump (Fig. 1). The quantity of this flow was measured with a precalibrated tubular flow probe incorporated in the bypass circuit (Micron Instruments, Los Angeles, Calif.). The revolutions of the roller pump controlled the degree of left ventricular bypass which was applied in random order at 0 (sham), 25, 33, 50, 75, and 100 per cent of the fixed cardiac output.

At the end of the experiment the heart was excised and Evans blue dye was injected into the coronary artery distal to the ligature. Immediately after injection, the stained left ventricular myocardium was excised and weighed for gross estimation of the non-perfused region. The total left ventricular weight was determined and used for indexing size of ischemic area, as well as coronary blood flow (CBFI), and myocardial oxygen consumption (MVO₂I) data, obtained before and after coronary artery ligation (CAO).

*Kindly provided by the Division of Artificial Organs, University of Utah, Salt Lake City, Utah.

Experimental protocol

After completion of the preparation at least 10 minutes were allowed for stabilization of all variables. Data were obtained at control, counterpulsation, and various percentages of left ventricular bypass interventions in random sequence. In the seven animals with pericoronary snare additional data were obtained after coronary artery ligation. The completeness of the ligation was assessed visually by observing the cyanotic dyskinetic region distal to the ligature. Ten to 15 minutes were allowed during each intervention for stabilization and data were not obtained unless coronary blood flow was stable for at least five minutes.

Linear regression and paired t test methods were used for statistical analysis. In order to derive the mean slope of per cent left ventricular bypass versus MVO index reduction, individual slopes (b) were weighted by the reciprocal square of their standard error ($1/SE_b$) then the sum of products ($\Sigma b/SE_b$) was divided by the sum of weights ($\Sigma 1/SE_b$). In order to compare the two techniques in terms of MVO reduction, the percentage of left heart bypass, which in the same animal produced the same reduction in MVO index as counterpulsation, was also determined from these regression equations.

Results

A. Counterpulsation

1 Effect on the intact left ventricle (Table I). MVO index decreased during counterpulsation in all experiments by an average of 1.53 ± 0.23 ml.O_2/min 100 g LV ($n = 20$, $p < 0.0001$) (Fig. 2). This MVO decrease was associated with increase of coronary sinus oxygen saturation. While there were small inconsistent changes in coronary blood flow index (CBFI) in the individual experiments, the control CBFI of 108.1 ± 9.6 mL/min 100 g LV increased to 111.4 ± 13.1 during counterpulsation thus for the group the 3.3 ± 5.0 mean change in coronary blood flow associated with counterpulsation was not significant. The left ventricular systolic pressure decreased by 34.3 ± 2.5 mm. Hg ($n = 20$, $p < 0.0001$) from 134.4 ± 3.1 mm Hg at control to 100.1 ± 4.3 during counterpulsation and left ventricular end diastolic pressure decreased by 0.5 ± 0.2 mm. Hg ($n = 20$, $p < 0.05$).

2 Comparison of effect before and after co

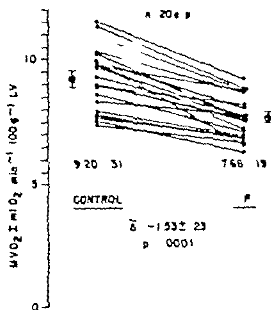


Fig. 2. Effect of counterpulsation on myocardial oxygen consumption. CP = counterpulsation; exp = experiments; MVO = myocardial oxygen consumption index.

Table I. Effect of counterpulsation on myocardial oxygen consumption index, coronary blood flow index, left ventricular end-diastolic pressure and left ventricular peak systolic pressure

		n = 20	Mean difference	p
MVO I	C	9.20 ± 0.31		
ml. O_2/min 100 g LV	CP	7.66 ± 0.19	−1.53 ± 0.23	<0.0001
CBFI	C	108.1 ± 9.6		
ml./min 100 g LV	CP	111.4 ± 13.1	+3.3 ± 5.0	N.S.
LVedp	C	9.0 ± 0.5		
mm. Hg	CP	8.5 ± 0.5	−0.5 ± 0.2	<0.05
LVSP	C	134.4 ± 3.1		
mm. Hg	CP	100.1 ± 4.3	−34.3 ± 2.5	<0.0001

Error terms are standard error of the mean.
Abbreviations: C = control, CBFI = coronary blood flow index; CP = counterpulsation, LVedp = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure, MVO,I = myocardial oxygen consumption index, N.S. = non-significant.

nary occlusion (Table II). In the seven animals in which data were obtained *before* and *after* coronary artery occlusion, myocardial oxygen consumption index decreased by 1.88 ± 0.30 mL O_2/min 100 g LV ($n = 7$, $p < 0.0007$) during counterpulsation before coronary artery occlusion and 1.82 ± 0.33 mL O_2/min 100 g LV ($n = 7$, $p < 0.00?$) after coronary artery occlusion. The

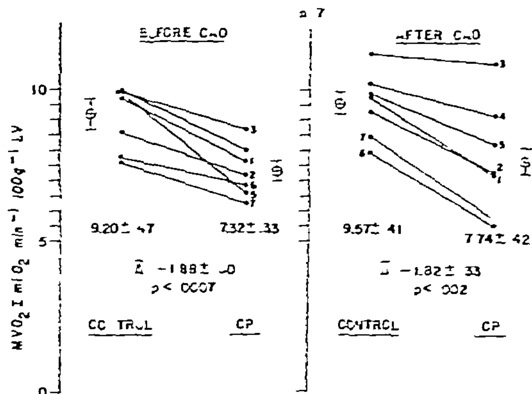


Fig. 3 Effect of counterpulsation on myocardial oxygen consumption before and after coronary artery occlusion. CAO = coronary artery occlusion; CP = counterpulsation; MVO$_2$I = myocardial oxygen consumption index.

Table II. Comparison of counterpulsation effect on myocardial oxygen consumption index, coronary blood flow index, left ventricular end-diastolic pressure, and left ventricular systolic pressure before and after coronary occlusion (n = 7)

		Control	CP	Mean difference	p
MVO$_2$I	C	9.20 ± 0.47	7.32 ± 0.33	−1.88 ± 0.40	< 0.007
(ml O$_2$ min^{-1} 100 g LV)	CAO	9.57 ± 0.41	7.74 ± 0.42	−1.82 ± 0.33	< 0.002
CBFI	C	[illegible] ± [illegible]	[illegible] ± [illegible]	−[illegible] ± 2.9	NS
(ml min^{-1} 100 g LV)	CAO	[illegible] ± [illegible]	[illegible] ± [illegible]	[illegible] ± 11.2	NS
LVedp	C	[illegible]	[illegible]	+0.1 ± 0.3	NS
(mm Hg)	CAO	11.5 ± 1.6	[illegible] ± 1.1	−1.0 ± 0.7	NS
LVSP	C	[illegible]	[illegible]	[illegible] ± 3.1	< [illegible]
(mm Hg)	CAO	[illegible]	[illegible]	[illegible]	< [illegible]

Abbreviations: C = before coronary occlusion; CAO = after coronary artery occlusion; CBFI = coronary blood flow index; CP = counterpulsation; LVedp = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; MVO$_2$I = myocardial oxygen consumption index; NS = not significant.

small difference in the control values of myocardial oxygen index before and after coronary artery occlusion (0.36 ± 0.14 ml O$_2$/min/100 g LV) was borderline significant. There was no significant difference in the MVO$_2$I index data obtained during counterpulsation before and after coronary artery occlusion (Fig. 3). Counterpulsation did not significantly alter coronary blood flow index either before or after coronary artery occlusion; however, coronary blood flow values after coronary occlusion were in general higher ($p < 0.05$) both during control and counterpulsation for time related reasons discussed in detail elsewhere.[11] In these seven experiments there was no significant reduction of left ventricular end-diastolic pressure by counterpulsation either before or after coronary artery occlusion. However, after coronary artery occlusion the left ventricular end-diastolic pressure was higher by 3.6 ± 1.3 mm Hg (n = 7, $p < 0.05$) in

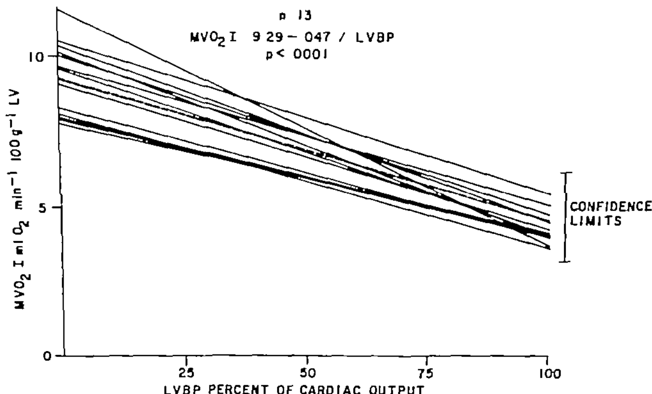


Fig. 4. Effect of left ventricular bypass on myocardial oxygen consumption. Individual *(solid)* and mean weighted *(broken)* regression lines obtained from 13 animals. Correlation coefficient of individual lines ranged between .93 and .98. Confidence limits are t 95 per cent level. *LVBP* = left ventricular bypass; *MVO_2I* = myocardial oxygen consumption index.

the control state and by 2.5 ± 0.7 mm. Hg (n = 7 $p < 0.02$) during counterpulsation. Left ventricular systolic pressure during counterpulsation following coronary artery occlusion decreased by 32.3 ± 0.7 mm. Hg (n = 7 $p < 0.0004$) comparable to the decrease before coronary artery occlusion. Control left ventricular systolic pressure was the same before and after coronary artery occlusion.

B Left ventricular bypass

1 Effect on the intact left ventricle. MVO index decreased linearly (r = .93 to .98) with increasing levels of left ventricular bypass expressed as per cent of the fixed cardiac output. The mean weighted slope of MVO index reduction was −0.047 ± 0.007 ml. O_2/min 100 g LV (n = 13, $p < 0.0001$, 95 per cent confidence limits (C.L.) = 0.032 to 0.063) per 1 per cent of left ventricular bypass (Fig. 4) Coronary blood flow index decreased significantly by 23.0 ± 4.8 and 26.8 ± 4.6 ml./100 g LV ($p < 0.001$ $p < 0.001$) only at higher (75 and 100 per cent) left ventricular bypass levels. The decrease of left ventricular systolic pressure with increasing levels of left ventricular bypass was linear (r = .86 to .99) with the mean weighted slope being −0.767 ± 0.12 mm. Hg (n = 13, $p < 0.001$, 95 per cent C.L. = 0.494 to 1.040) Left ventricular end-diastolic pressure fell with increasing levels of left ventricular bypass and the decrease bore a linear relationship (r = .67 to .99) The mean weighted slope was −0.053 ± 0.01 mm. Hg (n = 13, $p < 0.001$ 95 per cent C.L. = 0.030 to 0.075)

2. Comparison of effects before and after coronary artery occlusion. The effect of increasing levels of left ventricular bypass on MVO index in five animals which had left ventricular bypass runs at all levels (0, 33, 50, 75, and 100 per cent) both before and after coronary artery occlusion is shown in Fig. 5. By linear regression analysis and for each 1 per cent left ventricular bypass, MVO index was reduced by 0.045 ± 0.007 ml. O_2/min·100 g LV (n = 5 $p < 0.003$, 95 per cent C.L. = 0.026 to 0.036) before coronary artery occlusion and by 0.042 ± 0.006 ml. O_2/min 100 g LV (n = 5 $p < 0.002$, 95 per cent C.L. = 0.026 to 0.057) after coronary artery occlusion. The individual and mean weighted slopes were paral

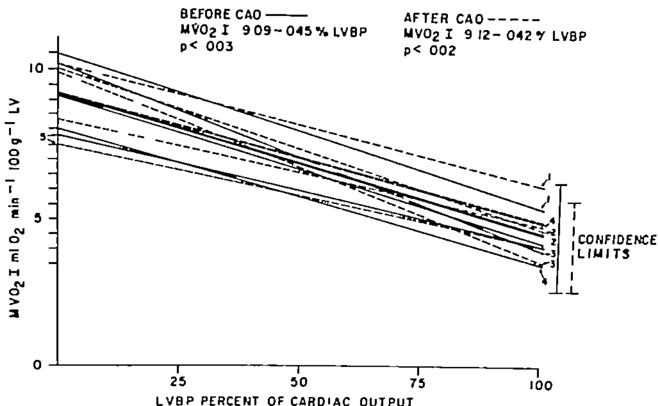


Fig. 5. Effect of left ventricular bypass on myocardial oxygen consumption before and after coronary artery occlusion. Control individual (*thin solid*) and mean weighted (*heavy solid*) regression lines obtained from 5 animals compared with individual (*thin broken*) and mean (*heavy broken*) regression lines obtained in the same animals after coronary artery occlusion. *Numbers* refer to individual animals. Correlation coefficient of all individual lines ranged between .83 to .98. Confidence limits are at the 95 per cent level. *CAO* = coronary artery occlusion, *LVBP* = left ventricular bypass; *MVO₂I* = myocardial oxygen consumption index.

lel. Although mean values of coronary blood flow index had good linear correlation with increasing degrees of left ventricular bypass, the individual slopes did not. The effect of left ventricular bypass on left ventricular systolic pressure before and after coronary artery occlusion was also evaluated by linear regression analysis. The reduction of left ventricular systolic pressure was 0.896 ± 0.14 mm. Hg (n = 5 $p < 0.004$ 95 per cent C.L. = 0.495 to 1.296) for each 1 per cent left ventricular bypass before coronary artery occlusion and 0.659 ± 0.07 mm. Hg (n = 5 $p < 0.001$ 95 per cent C.L. = 0.473 to 0.846) after coronary artery occlusion. Individual and mean weighted slopes were parallel. Left ventricular end-diastolic pressure values which were increased after coronary artery occlusion (see above) remained higher than corresponding control at 33 per cent left ventricular bypass by 2.5 ± 0.74 mm Hg (n = 4 $p < 0.05$) However at higher levels of left ventricular bypass, i.e. 50 75 and 100 per cent, there was no significant difference in the pre- and post-coronary artery occlusion values of left ventricular end-diastolic pressure. By increasing the level of left ventricular bypass, left ventricular end-diastolic pressure decreased by 0.054 ± 0.01 mm. Hg (n = 5 $p < 0.02$, 95 per cent C.L. = 0.020 to 0.087) for each 1 per cent left ventricular bypass coronary artery occlusion and by 0.061 ± 0.01 mm. Hg (n = 5 $p < 0.002$, 95 per cent C.L. = 0.040 to 0.083) after coronary artery occlusion. Individual and mean weighted slopes were again parallel.

C Comparison of MVO reduction effect by left ventricular bypass and counterpulsation. In Fig. 6, MVO_2 index reduction by counterpulsation and left ventricular bypass is compared in five animals in which both techniques were applied before and after coronary artery occlusion. Counterpulsation effect was found equivalent to 42 ± 7 per cent of left ventricular bypass before and 46 ± 9 per cent post-coronary artery occlusion.

In the seven animals with coronary occlusion

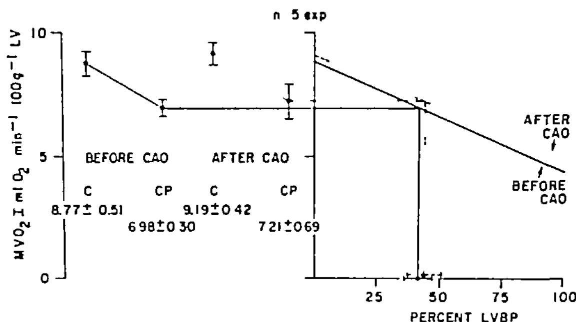


Fig. 6. Comparative effect on myocardial oxygen consumption of counterpulsation in terms of per cent bypass before (*solid lines*) and after (*broken lines*) coronary artery occlusion. *CAO* = coronary artery occlusion, *CP* = counterpulsation, *exp* = experiments, *LVBP* = left ventricular bypass, $\dot{M}VO_2I$ = myocardial oxygen consumption index.

the weight range (12 to 27 per cent) of the infarcted region as estimated by dye injection averaged 19.6 ± 2.7 per cent of the total left ventricular weight.

Discussion

The data reveal that maximal counterpulsation with intact left ventricle can decrease myocardial oxygen consumption by approximately 17 per cent as compared to over 50 per cent reduction achievable by complete left ventricular bypass. The reduction of myocardial oxygen consumption during counterpulsation resulted from reduced oxygen extraction rather than change in coronary blood flow. In this preparation with bypassed, vented right ventricle right coronary blood flow represents a small (5.2 per cent) of total coronary blood flow. Whether during counterpulsation the opposite changes of systolic and diastolic aortic pressure affected significantly this relationship is not known. In this study the magnitude of myocardial oxygen consumption reduction associated with counterpulsation compared with other studies results, at least in part, from using counterpulsation volume equal to stroke volume thus achieving optimal effect. Furthermore the extracorporeal circuit was considerably more rigid than the normal arterial system; therefore, the added compliance of the counterpulsating balloon had probably even greater effect in reducing left ventricular afterload. For these reasons it is possible that reductions of myocardial oxygen consumption of this magnitude may not be obtainable in clinical settings.

It has been suggested that elevated diastolic aortic pressure during counterpulsation increases coronary flow. However, whether the coronary vasculature adjusts its resistance by an autoregulatory response, or the coronary blood flow increases, depends to a considerable extent upon the existing coronary blood flow needs.[14] Thus, in well perfused and oxygenated hearts without excessive workload, as in this series, autoregulatory phenomena prevail. Powell and colleagues obtained results similar to ours regarding reduction of myocardial oxygen consumption and autoregulation of coronary blood flow in normotensive animals, while in a simulated shock state they found the improvement in cardiac performance to be flow-dependent. They concluded that decrease of myocardial oxygen consumption during counterpulsation is independent of coronary blood flow. Spotnitz and associates and Watson and co-workers have found an increase in coronary blood flow in normotensive canine preparations, while Leinbach and colleagues[15] have reported coronary blood flow autoregulation

in patients with cardiogenic shock. Watson and co-workers have pointed out that counterpulsation alters regional myocardial collateral coronary blood flow in the 20 minute period following the onset of counterpulsation, but according to Shaw and associates[20] with counterpulsation for longer periods, changes in collateral flow after coronary artery ligation may not occur

This conflicting information regarding effect of counterpulsation on coronary blood flow stems mostly from differences in experimental design. Thus although variables such as heart rate, and cardiac output were controlled, peripheral resistance has been allowed to vary [19] In this study heart rate, cardiac output, and systemic resistance were kept constant, therefore indirect effects were avoided. Moreover the systemic resistance and systemic arterial pressure were set at low normal levels and thus the effect of increased diastolic pressure during counterpulsation on coronary blood flow would not be obscured.

The absence of change in coronary blood flow despite increased coronary perfusion pressure during counterpulsation in this study appears to be due to coronary vasoconstriction metabolically mediated in response to reduction of myocardial oxygen consumption rather than to a purely myogenic autoregulatory mechanism. Thus the metabolic coronary vasoconstriction and the opposing increase in coronary perfusion pressure had insignificant net effect on coronary blood flow Whether this is a mere coincidence or the balanced result of reciprocal change between the decrease in developed left ventricular pressure in systole and the increase in transmyocardial pressure gradient in diastole is unclear The significant decrease of the systolic left ventricular pressure by 34.3 ± 2.5 mm. Hg during counterpulsation while all other variables including systemic resistance were kept constant, suggests that afterload reduction is the primary mechanism by which myocardial oxygen consumption is reduced.

An extracorporeal circuit was substituted for the normal arterial system in this study in order to allow independent control of capacitance and resistance, both of which contribute to aortic impedance. It has been suggested that systolic pressure is more sensitive to changes in systemic resistance than in arterial capacitance. Since the systemic resistance in this preparation was fixed, the change in peak left ventricular ejection pressure is probably due to alteration of the capacitance of the system resulting from the deflation of the balloon.

In this preparation with fixed steady state stroke volume, decreased aortic impedance generated by the balloon deflation before ventricular ejection results in immediate increase in ejection fraction leading to decreased left ventricular end-systolic volume. This leads to decreased left ventricular end-diastolic volume evidenced by a small but statistically significant drop in left ventricular end-diastolic pressure. Thus, the balloon counterpulsation effect may not be entirely based on afterload reduction but may involve, to a lesser degree, preload reduction as well. Whether reduction of aortic impedence leads also to improvement of contractility is difficult to ascertain because contractility assessments by left ventricular dp/dt are strongly affected by change of preload and afterload.

We showed previously that left ventricular myocardial oxygen consumption is unaffected by coronary artery occlusion in preparations with controlled external workload. This implies a compensatory increase in the oxygen consumption of the remaining viable myocardium. In this study the reduction of myocardial oxygen consumption by counterpulsation was the same before and after coronary ligations that resulted in 12 to 27 per cent functional loss of left ventricular myocardium. Therefore the fact that this counterpulsation effect was independent of the size of the non perfused region, implies that reduction of myocardial oxygen consumption involves the intact myocardium only

Previous studies showed a curvilinear relationship between level of bypass and myocardial oxygen consumption reduction,[4,6,16] suggesting that for a significant decrease in myocardial oxygen consumption almost total left ventricular bypass is required.

In contrast, our results show that the relationship of myocardial oxygen consumption reduction and per cent of left ventricular bypass is linear This difference may be explained on the basis of fixed systemic resistance. It is possible that systemic resistance unless controlled, may reflexly increase at the onset of the bypass, when volume and pressure waveform input into the arterial system are modified, leading to lesser than anticipated workload reduction. If such a

case arises during clinical application, pharmacological adjustment of arteriolar resistance may be in order The linear relationship of myocardial oxygen consumption to left ventricular bypass in our study is further supported by the similar relationship of left ventricular peak systolic pressure and left ventricular end-diastolic pressure decrease, both of which account for the reduction of myocardial oxygen consumption This reduction has been ascribed exclusively to preload reduction.[4-6] The linear decrease of left ventricular systolic pressure in this study where resistance did not change, shows that a substantial part of reduction of myocardial oxygen consumption may be ascribed to afterload decrease.

According to some reports complete left ventricular bypass cannot be attained unless the left ventricle is vented directly[23, 24] We found that in this preparation, with mean systemic aortic pressure above 60 mm. Hg, aortic valve opening and ventricular ejection are completely prevented because the left atrial vent of the bypass circuit is the pathway of lesser resistance. Thus with mean aortic pressure controlled at 70 mm. Hg initial adjustment of bypass flow setting the left ventricular peak systolic pressure at about 70 mm. Hg was followed by further decrease in this pressure, as the total left ventricular inflow was diverted to the pathway of lower resistance, i.e., of the bypass.

Coronary blood flow did not appear to change significantly at lower levels of left ventricular bypass. However at bypass levels of 75 and 100 per cent the values were significantly lower than control although the coronary perfusion (i.e, aortic pressure) was maintained constant. This demonstrates the ability of the coronary vascular bed to constrict in response to decreased metabolic demands despite maintenance or even increase of the transmyocardial pressure gradient. Whether the change of aortic pressure waveform by the bypass played a role cannot be assessed.

After coronary occlusion, reduction of myocardial oxygen consumption was not modified at any level of left ventricular bypass as compared to control. This is in accord with the data obtained during counterpulsation.

Data from five of the animals which had pre and post-coronary artery occlusion application of both methods, indicate that in terms of myocardial oxygen consumption reduction, maximal counterpulsation effect both before and after coronary occlusion is equivalent to approximately 45 per cent level of left ventricular bypass. Thus both assist methods may decrease myocardial oxygen consumption which theoretically could improve cardiac performance in a failing or ischemic heart. In this preparation, because of the relatively low systemic arterial resistance and pressure setting, increase of left ventricular end-diastolic pressure after major coronary artery occlusion, although substantial and statistically significant, did not exceed 12 mm. Hg. It is therefore unclear whether the relative magnitude and the quantitative relationship of effect of the two methods would remain unaltered at higher levels of left ventricular dysfunction. For this reason preparations with similar coronary artery occlusion are currently being studied at higher systemic resistance and pressure settings resulting in higher levels of left ventricular end diastolic pressure.

Whether reduction of myocardial oxygen consumption in the course of myocardial infarction affects the extent of ischemic necrosis has not been conclusively demonstrated. Thus rating circulatory assist methods on the basis of their ability to reduce myocardial oxygen consumption may not be the only criterion of their potential usefulness. For example, the increase of transmyocardial pressure gradient resulting from counterpulsation may be more important during cardiogenic shock than any reduction of myocardial oxygen consumption.[24]

Summary

In this preparation counterpulsation effect was found equivalent to 42 ± 7 per cent of complete left ventricular bypass before, and 46 ± 9 per cent post-coronary occlusion. We conclude that counterpulsation is effective mainly by reducing a major determinant of myocardial oxygen consumption, i.e., afterload, whereas left ventricular bypass by reducing primarily preload results in secondary afterload reduction when peripheral resistance is unchanged. At the higher left ventricular bypass levels, reduction of myocardial oxygen consumption is far greater than during balloon counterpulsation. Acute functional loss of myocardium does not alter the effect of these assist methods regarding the reduction of myocardial oxygen consumption. Whether selection of either method for clinical application

should be made only on the basis of its capability for reduction of myocardial oxygen consumption remains to be justified by conclusive demonstration of beneficial effect of reduction of myocardial oxygen consumption in the specific circulatory disorders.

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Case reports

Anomalous drainage of the right superior vena cava into the left atrium as an isolated anomaly Rare case report

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Anomalies of the great veins are not uncommon. Persistent left superior vena cava (LSVC) draining into the coronary sinus and right atrium is the most frequent type and is usually associated with a right superior vena cava (RSVC) placed in normal position. This anomaly does not cause any hemodynamic changes.

A persistent LSVC draining into the left atrium is uncommon and usually coexists with other important cardiac abnormalities, an atrial septal defect or single atrium being the most frequent ones.

Raghib and associates[1] described three cases of LSVC termination in the left atrium with atrial septal defect and absence of coronary sinus. These authors speculated that all these anomalies could have originated from a single anomalous developmental complex.

The persistence of the LSVC draining into the left atrium as an isolated anomaly with no other congenital cardiac defects and without RSVC is very rare. Tuchman and associates described the first case in a 15-year-old boy presenting cyanosis since early infancy Later Sherafat and colleagues[4] and Kabbani and co-workers have reported two other cases. A similar hemodynamic situation is created by an RSVC draining into the left atrium with no other concomitant abnormalities. Kirsch and associates reported the first case of this anomaly in a 2 year-old girl, who became cyanotic when 1 month old. Braudo and associates[1] and Wood described two other cases in girls. More recently Park and colleagues reported the first case in a female adult.

According to our survey of the literature we present in this case report the fifth case of this very rare congenital anomaly and the first case described in a male.

Case report

The patient, 7-month-old boy as admitted for cardiological evaluation because he showed cyanosis and murmur. After normal pregnancy labor as complicated by fetopelvic disproportion and the infant had to be delivered by cesarean section. The eight t birth was 3,200 grams. There was persistent cyanosis of the acral regions, that became generalized when crying had been noticed immediately after birth. He had never suffered hypoxic episodes, breathlessness during feeding, congestiv heart failure, or lower respiratory tract infections. Growth and dev lopment were normal. Physical examination revealed cyanosis of the fingers, without clubbing, and 2/6 ejection systolic murmur over the upper and mid-left sternal borders. No other disturbances were found. The electrocardiogram revealed left axis deviation (QRS angle −15 degrees) and left entricular enlargement. The chest film showed slight cardiomegaly caused by left ventricular enlargement, and decreased pulmonary supply Methemoglobin could not be demonstrated in blood. A clinical diagnosis of right to-left shunt could be established on these data. Cardiac catheterization was performed to locat the shunt. A catheter was introduced through the right saphenous ein and the inferior ena cava into the right trium. The catheter could not be passed into the superior ena cava from the right atrium. The trial septum was crossed through the foramen ovale and the catheter was introduced into the left atrium and superior ena cava. As presented in Table I, the oxygen saturation t the left trium and left entricle was only 80 per cent. The pressures in the right entricle and pulmonary artery were normal. I jection of radiopaque material into the superior ena ca a, right entricle, and left ventricle demonstrated normally placed right-sided superior ena ca a draining into the left atrium. The contrast solution

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Fig. 1 Venous angiocardiogram show the anomalous drainage of the right superior vena ca a into the left atrium. Anteroposterior projection.

passed via the left entricle t the aorta. N anomalous connection between the right and left chambers of the heart could be demonstrated. The pulmonary veins entered the left trium at the normal place. The contrast sol tion from the inferior vena cava passed t normal right entricle and pulmonary arteries. There was no evidence of persistent LSVC (Figs. 1 and 2). The patient has been followed for 2 years and his clinical situation has remained unchanged. His current growth and development are normal. Surgical correction has not yet been attempted.

Discussion

While the development of the venae cavae is well understood, the embryology of the RSVC draining into the left atrium remains unclear. As suggested by Kirsch and colleagues, a malposition of the right horn of the sinus venosus with a left and cephalic distortion associated with a normally developed interatrial septum would explain this condition. The aperture of the superior vena cava would be forced to be placed over the left atrium. The place of drainage of the coronary sinus remains unclear.

About one-third of the venous return is carried via the superior vena cava and the other two-thirds via the inferior vena cava. The basic hemodynamic disturbance common to isolated right or left SVC draining into the left atrium consists in an increased blood flow through the left-sided chambers, a decreased flow through the right-sided chambers, and a partial bypass of the lungs. [12] The systemic oxygen saturation is reduced, producing clinical cyanosis.

The right to-left shunt of both pathological syndromes is generally well tolerated. In the cases



Fig. 2. Venous angiocardiogram. Lateral projection. S legend to *Fig. 1* for details.

reported by Tuchman and co-workers[1] and b Park and associates, the patients were practical ly asymptomatic until early adolescence an adulthood. A mild cyanosis without any seriou manifestations of cardiopulmonar disease is near ly the only symptom present.[13] Digital clubbin and shortness of breath can develop, but conges tive heart failure episodes are rare. Norma growth and development have been reported i several cases, although poor physical develop ment can occur. One case of brain abscess ha been described as a complication.

A soft systolic murmur was heard over the left sternal border in our patient and in the case reported by Braudo and colleagues, but a cardiac murmur may not be present. Chest films usual ly show a heart of normal size or a moderate left ventricular enlargement. The pulmonary vascularity is always normal. The electrocardiogram suggests a left ventricular hypertrophy[3] or is normal.

The differential diagnosis of a cyanosis occurring in a normally developed infant includes primary lung disease, pulmonary arteriovenous fistula, methemoglobinemia and other hemoglobinopathies. The performance of an angiohemodynamic exploration is necessary in order to do a proper diagnosis. If the catheterization is via the

Table 1 Cardiac catheterization data

	SVC*	IVC	RA	PV	LA	LV	PA	RPA	LPA	RV
Oxygen saturation (%)	48	58	59	95	82-76	60	5	57	51	54
Pressure (mm. Hg)	mean 9		mean 6	a 16 v 10 mean 12	mean 6	66/2-10	18/8 mean 14	15/6 mean 10	16/7 mean 11	24/?-6

Abbreviations: SVC = superior vena cava, IVC = inferior vena cava, RA right atrium, PV = pulmonary vein, LA = left atrium, LV = left ventricle PA = pulmonary artery RPA = right pulmonary artery LPA = left pulmonary artery RV = right ventricle.

saphenous vein the catheter does not pass to the superior vena cava if it is via the cubital vein the contrast solution goes into the left atrium filling the aorta. The superior vena cava can be enlarged and the right atrium can be smaller than normal. Usually the drainage of the pulmonary veins is normal as in our case sometimes a slight displacement of these veins, caused by the abnormal drainage of the RSVC can be found. There is no left to-right shunt and the pulmonary pressure is always normal.

Surgical treatment of the RSVC *draining into* the left atrium consists in changing the flow of the RSVC into the right atrium. A successful surgical correction was obtained in the cases reported by Kirsch and colleagues[2] and by Braudo and associates, when the infants were 2 and 3 years old, respectively The repair of the LSVC draining in the left atrium needs more complex surgical techniques.[14, 15] The case reported by Sherafat and associates[6] needed a second operation. *Surgical repair has been delayed in our case* for there is no vital risk and a higher patient weight increases the long term possibilities of success.

Summary

A case of cyanotic congenital heart disease with left ventricular hypertrophy is described. Cardiac catheterization showed a right superior vena cava draining into the left atrium without other cardiovascular abnormality This is the fifth case of this rare congenital anomaly described in the literature *and the first one reported in a male.* The patient was 7-months-old when diagnosed. Despite the important right to-left shunt after a follow-up of 2 years, growth and development are normal.

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Echocardiographic diagnosis of pulmonary atresia with intact ventricular septum

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Pulmonary atresia with intact ventricular septum presents with extreme cyanosis in infancy. Pulmonary blood supply is through a ductus arteriosus and death occurs if the ductus closes before an adequate bronchial circulation develops.

Echocardiography is a simple non invasive diagnostic technique in the critically ill cyanotic neonate. Abnormal pulmonary valve movement may suggest the diagnosis of pulmonary stenosis[1-4] or pulmonary hypertension, while the echocardiogram also provides vital information about the size of the right ventricle, the relationship and relative size of the great arteries, and the spatial relationships between aorta, anterior mitral leaflet, and the interventricular septum.

The echocardiographic features of pulmonary atresia with intact septum have been reported as part of the hypoplastic right heart syndrome—a diminutive right ventricular dimension, normal to large left heart structures, and in some patients a hypoplastic and deformed tricuspid valve echo. This report discribes the echocardiographic features of the less common form of pulmonary atresia with intact ventricular septum, i.e., with a normally developed right ventricle and tricuspid valve. The echocardiographic features of this form of the syndrome have not, to our knowledge, been reported. The diagnosis was confirmed by cardiac catheterization, angiography and operation.

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Case report

The echocardiograms were made in a severely cyanotic and critically ill neonate aged 10 hours. Pregnancy and delivery were normal and the infant weighed 3.4 kilograms at birth. Physical examination revealed a severely cyanotic and dyspneic child with normal pulses. He had a prominent right ventricular lift with a systolic murmur of tricuspid incompetence along the left lower sternal border. The second heart sound was single. The electrocardiogram showed right atrial enlargement, right ventricular hypertrophy, and right axis deviation. The chest x-ray showed a large right ventricle and right atrium with a small pulmonary artery and pulmonary oligemia.

Echocardiographic findings. The echocardiogram was recorded using an Ekoline 20A echocardiograph coupled to an Electronics for Medicine VR-6 photographic recorder. A 5 MHz pediatric transducer was used and all the tracings were obtained with the transducer in standard positions along the left sternal border.

Fig. 1 shows an M-mode scan in the long axis of the heart made by directing the transducer progressively inferolaterally to show cardiac structures from the aorta to the apex of the heart. The transducer was kept in the third left intercostal space. The aortic root was normal in size and the aortic leaflets moved normally. Left atrial diameter was normal (Table I). The interventricular septum was present and thickened (Fig. 2). The left ventricle was normal in size (diastolic diameter 19 mm.) with good systolic function and the right ventricular diameter was slightly decreased (8 mm.). There was severe right ventricular hypertrophy with thick right ventricular anterior wall and interventricular septum (Fig. 2 and Table I). The right ventricular outflow tract was well shown anterior to the ascending aorta. The aorta did not override the interventricular septum, its anterior wall was continuous with the septum. The posterior aortic wall was continuous with the anterior leaflet of the mitral valve. The tricuspid valve showed decreased excursion (Fig. 3). This pattern suggests decreased flow through the valve, while the prolonged AC time suggests a high right ventricular end-

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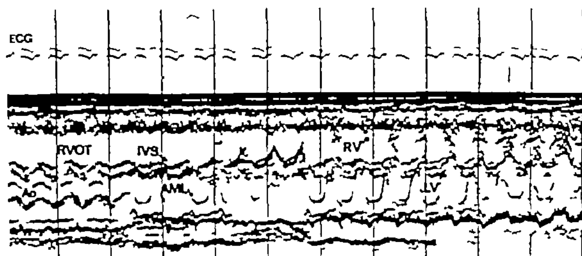


Fig. 1. M-mode scan made from the third left intercostal space by directing the transducer progressively inferolaterally. The aorta *(Ao)*, interventricular septum *(IVS)*, and both left *(LV)* and right *(RV)* entricles are shown. The right entricle and its outflow tract *(RVOT)* are relatively normal in size. The anterior aortic wall is continuous with the interventricular septum and the posterior aortic wall is continuous with the anterior mitral leaflet *(AML)*.

Table I. Echocardiographic measurements

	Patient	*Normal alue according to right*
LV diameter (end-diastole) (mm.)	19	19-20
RV diameter (mm.)	6	13-14
LA diameter (mm.)	12	9-10
Ao root diameter (mm.)	12	11-12
Anterior RV wall thickness (mm.)	7	2.5-2.7
Interventricular septum (mm.)	7	3.2-3.5
LV posterior wall thickness (mm.)	3.5	3.2-3.5

Abbreviations: Ao = aorta, LA left atrium, LV = left entricle, RV right ventricle.

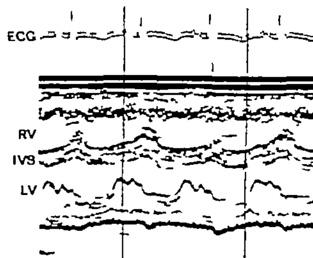


Fig. 2. Echocardiogram showing right entricular *(RV)* hypertrophy and slightly decreased RV diameter.

diastolic pressure, although it is possible that for technical reasons the maximum amplitude of excursion of the al was not seen.

The pulmonary al as recorded by directing the transducer superiorly and to the left from the third left intercostal space (Fig. 4*A*) or by directing it directly posteriorly from the second left intercostal space (Fig. 4*B*). The pulmonary alv echocardiogram showed giant pre-systolic wa with maximum amplitude of 9 mm. The alv then returned to its diastolic position without opening during ventricular systole and remained in that position for the remainder of the cardiac cycle (Fig. 4*B*).

The echocardiographic diagnosis as pulmonary atresia with intact entricular septum.

Cardiac catheterization and angiography. Cardiac catheterization confirmed the clinical and echocardiographic diagnosis. A enous catheter as passed from the right trium to the right entricle but could not be manipulated into the pulmonary artery. The left trium was entered by patent foramen ovale and the catheter was then passed into the pulmonary ein and also the left entricle. The right entricular pressure was 120/4-12 mm. Hg and the right atrial mean pressure 4 mm. Hg with large w of 8 mm. Hg; systemic arterial pressure was 68/64 mm. Hg. Blood sampling showed an arterial oxygen saturation of 50 per cent and right-to-left shunt of 81 per cent.

Angiography was typical for pulmonary atresia with intact entricular septum. The right entricle and its outflow tract were normal in size and there was moderate tricuspid incompetence. There was complete pulmonary valvar obstruction. The interventricular septum was intact, contrast medium passed from right atrium to left atrium through patent

Review

The cardiac impulse A new look at an old art

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"As to his heart is in its place, this means that the fatty mass of the heart is in his left side it does not go upwards and does not fall downwards. (Eb 856) 1600 B.C

Palpation of the cardiac impulse is as ancient as the evolution of the art of medical practice Ancient Egyptain physicians and priests used to evaluate cardiac disease by palpating the heart and all the peripheral pulses. This is portrayed in the Ebers papyrus, which carries the date of Amenophis I (1550 B.C.) In this treatise the chapter called "Beginning of the secret of the Physician knowledge of the heart s movement and knowledge of the heart" (Eb 854) starts as follows "there are vessels from it to every limb As to this, when any physician applies his hands or his fingers upon the head, upon the back of the head, upon the two hands, upon the pulse, upon the feet, and *upon the place of the heart* He says measure the heart in order to recognize the indications that have arisen therein." A variety of cardiac disease is described in this historic monograph. An illness called the "heart's dancing" "this means that it moves from its place" a displaced heart "His heart has made a little going downwards" "The escape of the heart the "Heart prick and "Forgetfulness of the heart" were mentioned.

Over the centuries thereafter precordial palpation continued to be an integral part of cardiac evaluation and usually was performed with the physician sitting and facing the patient standing.

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Recording of the cardiac impulse found substantial popularity in the nineteenth century in Europe[1-4] and has contributed to our understanding of cardiac physiology utilizing animal (Fig. 1) and human studies. These studies were made possible through the recording method developed by Marey Later Sir James McKenzie[6] elaborated on the value of cardiac impulse and venous and carotid pulse recording in his famous monograph entitled "The study of the pulse arterial, venous and hepatic and of the movements of the heart" published in 1902. This monograph provides a most thorough description of the "movements of the heart in health and in disease"[7] and continues to be an important landmark in our understanding of the events constituting the apical and left parasternal cardiac impulse (Fig. 2)

Since then, many workers have attempted to refine and standardize cardiac impulse recording techniques, or to utilize various quantitative measures to enhance the diagnostic value of the recorded cardiac impulse.[8-44]

However there seems to be a declining interest in research in this area and a tendency for young physicians and medical students to view the art of cardiac palpation as being obsolete and unworthy of careful study Factors responsible for this phenomenon include

1 The growth of medical technology has provided other "noninvasive" means of assessment of heart disease. The ease by which information can be obtained from an *adequate* echocardiogram cardiac roentgenogram, and the electrocardiogram far exceed in value and accuracy any information obtained from a *hasty* bedside *examination of the heart.*

2. Many of the initial reports attempting to quantitate cardiac impulse recording and corre-

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1st Cardiac Revolution. 2d Cardiac Revolution. 3d Cardiac Revolution. 4th Cardiac Revolution.

N°1 N°2 N°3

Fig 1 A reproduction of Fig. 7 from the chapter of Examination of the Movements of the Heart by Automatic Apparatus by Paul Constantin (1884). The recordings were obtained from horse using the Marey recording device. The description of the figure as included in the text. "represents the traces of the right auricle (No. 1), the right ventricle (No. 2) and the cardiac pulsation (No. 3) taken simultaneously during four complete revolutions of the heart, with scale which permits the measurement in fractions of second of the duration of the briefest movements of the organ.

late it with hemodynamic data have failed to stand the test of time. Since we live in an era that gives credibility only to numbers, tests lending qualitative rather than quantitative information are generally considered outmoded and incompletely reliable.

3. Uncertainty about what constitutes the "apical" and "left parasternal impulse." Traditionally they have been referred to as the left ventricular" and "right ventricular" impulses, respectively and their recordings have been termed "left ventricular" and "right ventricular" apexcardiograms. However studies comparing the site of external recordings of what is clinically perceived as the cardiac apex with angiographic findings have shown that the apical impulse may correspond to the left ventricular apical or supra-apical region and may even represent part of the right ventricle in patients with right ventricular dilatation and clockwise rotation of the heart.[7] Similarly a systolic lift in the left



Fig 2. A reproduction of Fig. 30 of Sir James McKenzie "The Movement of the Heart in Health and in Disease. The original legend reads: "Simultaneous tracings of the heart movements *(upper tracing)* and of the radial pulse. The first part of the upper tracing was taken from the apex beat in the fourth interspace immediately outside the nipple, while the latter part was taken in the same interspace near the left border of the sternum. In the first part the cardiogram show systolic plateau during the ventricular outflow *(E)*. In the other part the cardiogram is inverted, ie., there is depression during this period *(E)*.

parasternal region need not necessarily be due to right ventricular enlargement since it could be produced by a variety of other causes including mitral regurgitation and anterior wall dyskinesia.

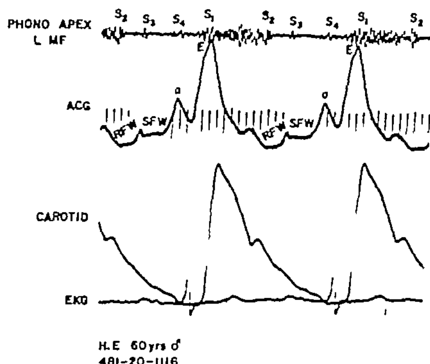


Fig. 3. Recordings from a patient with severe mitral regurgitation due t ruptured chordae tendineae of the posterior leaflet. In this patient, the systolic murmur was loudest over the aortic area. The pexcardiogram shows a hyperkinetic apical impulse that peaks in early systole and the carotid upstroke is rapid, these features differentiate this case from aortic stenosis. Also, note the prominent presystolic w at the apical impulse characteristic of acute mitral regurgitation. Abbreviations. *Phono.* (phonocardiogram); *L-MF* (low-to-medium frequency); *ACG* (pexcardiogram); *RFW* (rapid filling wav); *SFW* (slow filling wave; *a* (presystolic wave), *E* (early outward movement); *EKG* (electrocardiogram).

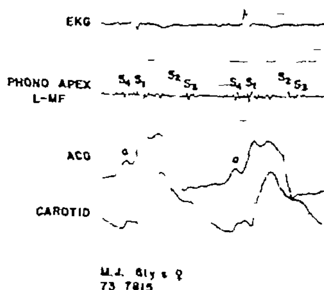


Fig. 4 Recordings from pa ien h severe myocardial disease. The pexcardiogram show p minent presystolic wave (*a*) that corresponds t he fourth heart sound (S_4) in the phonocardiogram. The lef en ric lar end diastolic pressure as 34 mm. Hg.

4. Difficulty in the timing of events, appreciated by precordial palpation, in relation to the cardiac cycle is a major handicap for the clinical bedside interpretation of the cardiac impulse. For example, a double outward impulse at the apex could theoretically represent a presystolic and a systolic wave (Figs. 3, 4, and 5) double systolic hump (Fig. 9) or a systolic and a middiastolic outward lift (Fig. 20). In the absence of a reliable reference such as an electrocardiogram, various observers may differ in interpreting the same findings on mere palpation.

5. Recording of the cardiac impulse is difficult to standardize. The apexcardiogram wave configuration does not only depend upon its basic characteristics and the site of recording but also upon the type of the recording device, its range of sensitivity and time constant, as well as the degree of counterpressure applied to the transducer and its angle of tilt in relation to the chest wall.

6. Lack of reproducibility of impulse recording, related in part to many of the foregoing factors,

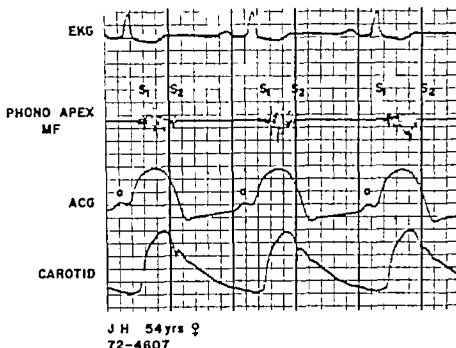


Fig. 6. Tracings from patient with severe aortic stenosis. The apexcardiogram shows prominent presystolic in addition to heaving apical impulse that peaks in midsystole. However the phonocardiogram does not show recordable fourth heart sound.

has limited the value of apexcardiography as a research tool, and as a reliable means in the follow up of patients.

In spite of these and possible other problems, precordial palpation and cardiac impulse recording continue to be useful tools in the beside evaluation of heart disease. In order to utilize it effectively the clinical observer should be aware of its limitations, and develop his skill through careful correlation with hemodynamic and other clinical and laboratory findings.

Today's student might question the value of such tedious exercise. However none of the new techniques is without fault and, in addition, each involves expense, inconvenience, and even risk to the patient, a good physician should strive to achieve adequate patient evaluation with the least possible expense, inconvenience, and risk.

After this rather long prelude, it is appropriate to provide a critical review of precordial palpation in the light of our recent knowledge.

The apical impulse

In the absence of significant chest deformity or pleuropulmonary disease the location of the outermost, lowermost point of palpable apical pulsation tells about the over-all heart size. In cardiac patients with disease imposing *increased pressure load* such as aortic stenosis or systemic hypertension, mild-to-moderate cardiac enlargement is often due to increased left ventricular muscle mass. However marked cardiac enlargement almost always signifies poor left ventricular performance manifest in decreased left ventricular ejection fraction and increased ventricular volume. Therefore, in patients with isolated aortic stenosis, the over all heart size detected by palpation or by x ray examination correlates poorly with the severity of stenosis.[44]

In patients with primary myocardial or ischemic heart disease, the increase in heart size has similar implications, the degree of cardiac dilatation generally has an inverse relationship to ventricular performance.

In cardiac patients with disease imposing *increased volume load*, such as with aortic or mitral valve incompetence, the cardiac size primarily reflects the magnitude of valvular incompetence but also is influenced by the degree of impairment of ventricular function. Other clinical and/or laboratory findings help to establish the contribution of each of these two components to cardiac enlargement.

The commonly used classification of the

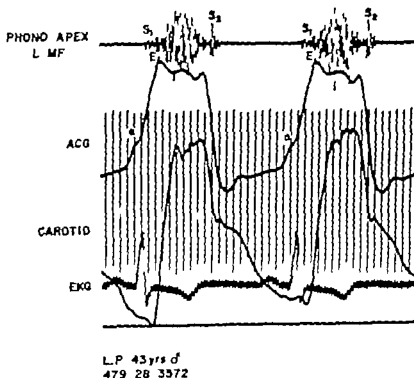


Fig. 6. Tracings from a patient with severe aortic stenosis due t a calcified bicuspid aortic valve. Note that the strong presystolic w e *(a)* in the apexcardiogram merges with the systolic apical bea e; thereby it could not be appreciated on palpation. P R interval = 0.14 sec.

patterns of a forceful apical impluse into "hyper kinetic, signifying volume overload, and "heav ing and/or sustained," signifying pressure over load of the left ventricle, is simplistic and occasionally misleading. It is true that an apical impulse showing an early systolic outward lift that promptly recedes away from the chest wall is rarely seen with significant longstanding increase in pressure load. Besides volume overload of the left ventricle a hyperkinetic apical impulse is encountered in anxious but otherwise normal individuals, in thyroid hyperfunction, and in the early stages of systemic hypertension.[41, 44] A hy perkinetic apical impulse favors mitral incompe tence over aortic stenosis when the radiation of the systolic murmur is atypical and could be confusing (Fig 3) On the other hand, a sustained apical impulse need not necessarily mean increased left ventricular pressure load. It is encountered most dramatically in patients with combined left entricular lume and pressure overload, such as aortic valv disease with both stenosis and incompet n In addition a sustained apical impulse is frequently encoun tered in patients ith markedly di ted hearts as a result of advanced myocardial disease, or in patients with prior myocardial infarction when the examiner palpates over an area with dyski netic ventricular wall motion. Furthermore, a "heaving" apical impulse could be artifactually produced by asking the patient to turn on his left side (bringing the apical impulse to the examin er's hand) particularly in individuals with thin chest wall. Conversely patients with thick chest walls and those with significant obstructive pulmonary disease could have significant cardiac enlargement that cannot be appreciated on precordial palpation.

A prominent presystolic "kick is often felt on palpating the cardiac apex with the patient turned on the left side and the respiration held in the appropriate stage of expiration allowing maximum appreciation of the apical impulse. A strong presystolic wave usually signifies elevated left ventricular end-diastolic pressure a presys tolic wave exceeding 15 per cent of the total amplitude of the recorded apical impulse or 40 per cent of the total diastolic filling phase usually corresponds to a left ventricular end-diastolic pressure in excess of 18 mm. Hg.[44-72] Furthermore

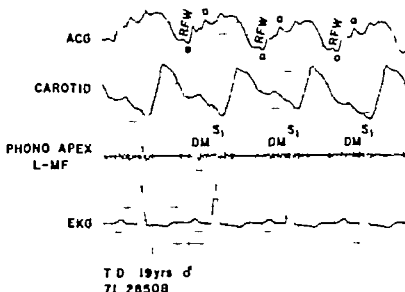


Fig 7 Recordings from patient with severe aortic alv incompetence and heart failure. The phonocardiogram show low frequency murmur in late diastole. The apexcardiogram show prominent presystolic ( ) indicating that the low frequency murmur is an Austin-Flint murmur and *not* due to associated mitral al stenosis. Abbreviations As in Fig. 3; *O* (the zero point of the apexcardiogram); *DM* (diastolic murmur).

a palpable forceful presystolic wave, reflecting strong left atrial contraction, is a much more reliable bedside sign of left ventricular disease than an "audible" fourth heart sound. In addition, there are numerous problems regarding the auscultatory appreciation of a fourth heart sound, and in many instances a normally split *first heart sound is misinterpreted as being* composed of an S and an S_1

Our experience conforms with that of other workers in that a strong presystolic apical kick is often seen without an audible fourth heart sound in patients with left ventricular disease (Figs. 4 and 5) Furthermore, as a rule a loud S is accompanied by a palpable atrial kick, except, perhaps, in patients in whom the apical impulse could not be palpated and in those with a short P R interval. In that circumstance the presystolic wave merges with the systolic apical impulse, thereby the two waves are perceived clinically as a single systolic" wave (Fig. 6).

In patients with borderline left ventricular dysfunction and normal apical impulse pattern at rest, a strong presystolic kick could be produced by a sustained handgrip exercise. However isometric exercise often leads to exaggeration of the presystolic wave in normal individuals and it

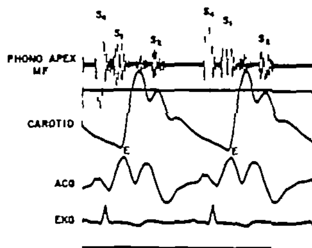


Fig. 8. Tracings from patient with idiopathic hypertrophic subaortic stenosis. The apexcardiogram is characterized by three positive waves (trifid). The first wave is presystolic wave corresponding to the left atrial "kick, the second is an early systolic wave, and the third is late systolic wave corresponding to the outflow tract obstruction leading to increase in the left ventricular systolic pressure. In addition, the fourth heart sound in this particular patient was louder than the first heart sound and was misinterpreted t auscultation as loud first heart sound followed by an jection click.

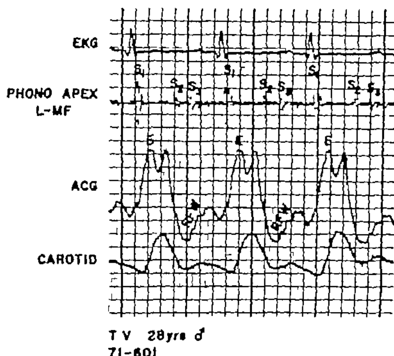


Fig. 9 Recordings from a patient with heart failure due to radiation-induced myocardial disease. The apical impulse has two positive systolic waves. Also, note that the rapid filling phase is interrupted by multiple deceleration waves corresponding to components of the third heart sound.

has been sometimes difficult, in our experience, to differentiate the "normal" from the "abnormal" response.

A palpable presystolic wave at the apex almost excludes the possibility of significant mitral stenosis.[13] Recognition of this fact is of particular importance in the clinical differentiation of the Austin Flint murmur" from that due to coexistent mitral stenosis in patients with aortic incompetence associated with a low frequency presystolic apical murmur[44] (Fig. 7)

A trifid apical impulse with one presystolic and two systolic positive waves, is typically seen with idiopathic hypertrophic subaortic stenosis[45] (Fig. 8) we have encountered this pattern in 17 of 24 patients with IHSS The presystolic wave represent forceful left atrial contraction and the early systolic wave corresponds to the early phase of left ventricular ejection, while the last systolic wave is the result of left ventricular outflow obstruction and increased left ventricular systolic pressure. Occasionally we have encountered the same "trifid pattern in patients with severe aortic valve stenosis A slow carotid pulse upstroke and other clinical findings help to identify the latter condition. On the other hand, the apical impulse in IHSS sometimes shows only two positive waves, a presystolic and systolic or two systolic positive waves. It should be emphasized, however that double systolic humps are encountered in a variety of conditions besides IHSS. The list includes normal individuals, fixed orifice aortic stenosis, ischemic heart disease with anterior wall dyskinesia, and myocardial disease (Fig. 9) Because this pattern can be misinterpreted on palpation as representing an atrial kick in addition to a systolic wave, simultaneous apical impulse and ECG recording is often required to reveal the details of the wave pattern.

Attempts to quantitate the diastolic rapid filling phase in the apexcardiogram and to utilize it for purposes of quantitation of mitral regurgitation[33, 34, 46] and exclusion of significant mitral stenosis[47] have produced useful data. However this requires high quality apexcardiograms and the changes are infrequently appreciated readily by the palpating fingers. On the other hand, an abrupt deceleration wave during the left ventricular filling phase is often appreciated on palpation and provides a bedside clue towards the diagnosis of pedunculated left atrial myxoma.[48]



Fig. 10. Recordings at the left parasternal area from normal individual. The left parasternal cardiogram (*LPC*) is characterized by notched early systolic outward movement th one component preceding the first sound (*E*), and the other following the first sound (*E'*). This is followed by gentle movement way from the chest all occupying the rest of the systole and the early part of diastole Tracings ha been retouched.

A palpable diastolic deceleration wave corresponds to an audible tumor plop sound.

The left parasternal impulse

The left parasternal impulse is often referred to as the right ventricular impulse. Several investigators have correlated the left parasternal pulsation with right ventricular pressure changes showing impressive illustrations in certain instances.

The normal left parasternal impulse is characterized by a gentle early systolic outward movement followed by retraction away from the chest wall occupying the latter part of systole and early part of diastole until the opening of the tricuspid valve (Fig. 10)

Prominent systolic pulsations in the left parasternal region may be seen in normal individuals with decreased anteroposterior diameter of the chest (depressed sternum or straight back) in right ventricular enlargement, with left atrial dilatation and with dyskinesia of the anterior wall of the left ventricle or of the interventricular septum.

Right ventricular volume overload typically produces active rocking movement in the left parasternal region. This pattern is seen with pretricuspid left to-right shunt (atrial septal defect or anomalous pulmonary venous drainage) and with significant tricuspid regurgitation. Although the rocking movement is usually referred to as systolic," careful examination of left parasternal impulse recordings often reveals that the outward motion starts in diastole with the onset of right ventricular filling and peaks in early systole, to be followed by a rapid negative wave (movement away from the chest wall) during the right ventricular systolic ejection phase. In other words, volume overload of the right ventricle leads to an exaggeration of the normal left parasternal motion pattern, the degree of "rocking" generally reflects the magnitude of the volume overload (Figs. 11 and 12) We have encountered this typical pattern in two-thirds (18 of 27) of cases with significant pretricuspid shunts in the absence of increased pulmonary vascular resistance.

With increased right ventricular pressure load, the left parasternal impulse is characterized by a gentle systolic "heave that peaks in early to-

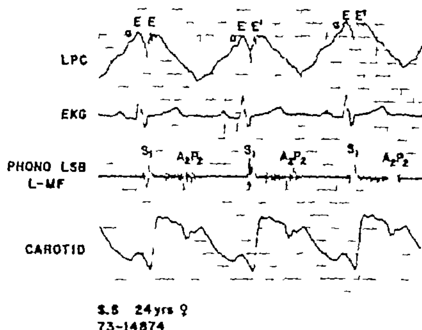


Fig. 11 Tracings from a patient with a large secundum trial septal defect and normal pulmonary artery pressure. The left parasternal cardiogram is characterized by a rocking movement, the positive part of which peaks in early systole and the negative part corresponds to early diastole. Abbreviations: *A* (aortic component of the second heart sound) *P* (pulmonic component of the second heart sound) *LSB* (left sternal border).

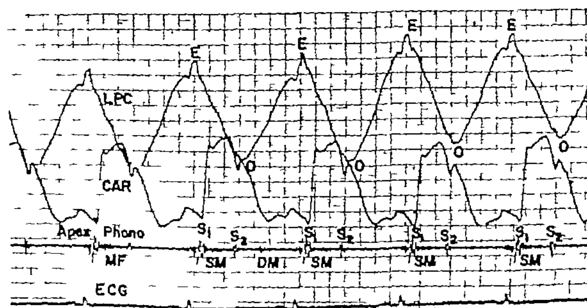


Fig. 12. Recordings from patient ith severe tricuspid regurgitation due to carcinoid heart disease. Note the rocking movement in the left parasternal cardiogram with a positive wave peaking in early systole and negative w ve reaching its maxim m earl diastole. *SM* = systolic murmur

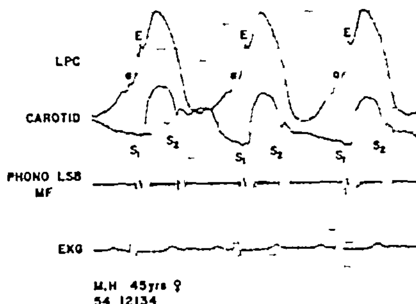


Fig. 13 Recordings from patient with Fallot tetralogy The left parasternal cardiogram show systolic lea that peaks in midsystole.

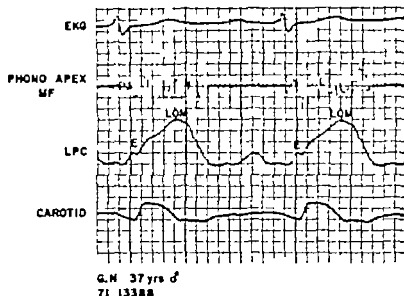


Fig. 14 Recordings from patient with acute severe mitral regurgitation due to ruptured chordae tendineae. The left parasternal movement is characterized by an outward movement that peaks in late systole. This movement has been designed the left atrial lift and is probably due to systolic expansion of the left atrium caused by blood regurgitating through the mitral valve. *LOM* = late outward movement.

midsystole such is typically seen in Fallot's tetralogy and with pulmonary hypertension (Fig. 13). In the latter condition, a prominent presystolic kick representing a forceful right atrial contraction is often palpable, particularly in patients with a long P R interval.

In mitral regurgitation the left atrium represents an expansile cushion lying under the heart. In systole, as the left atrium expands in volume, it lifts the heart anteriorly against the chest wall, thereby producing a systolic left parasternal lift that peaks in late systole[43, 44, 45] (Fig. 14) It is remarkable that the recorded left parasternal movement often parallels the left

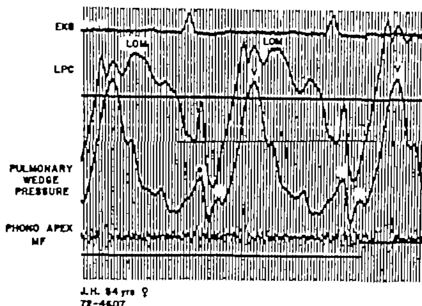


Fig. 15. Simultaneous electrocardiogram, left parasternal cardiogram, pulmonary wedge pressure tracing, and apical phonocardiogram from a patient with ruptured chordae tendineae causing severe mitral regurgitation. Note the parallelism between the left parasternal movement and the V wave in the wedge pressure tracing. The time difference between the onset of the V wave in the pressure tracing and the recording in the left parasternal cardiogram can be accounted for by the delay in the pressure transmission through the Swan-Ganz catheter. Time lines are at 10 msec.

atrial pressure curve, particularly in patients with acute mitral regurgitation such as with ruptured chordae tendineae (Fig. 15). In these patients, the left parasternal impulse recording often provides a useful clue to the severity of mitral regurgitation.[43]

During an attack of angina pectoris accompanied by anterior wall ischemia, a prominent late systolic bulge representing anterior wall dyskinesia, may be felt transiently during the pain attack. The left parasternal impulse reverts to normal with the relief of pain (Fig. 16). Such a finding provides a sure clinical evidence to the ischemic etiology of pain. Similarly, patients with anterior wall dyskinesia from prior myocardial infarction may exhibit an area of sustained systolic (Fig. 17) or late systolic bulge, the site of which generally corresponds to the site of prior infarction.[44, 45] However, late systolic anterior wall lift may be seen, also, with large posterior myocardial aneurysms: the distending aneurysmal sac lifts the heart towards the chest wall during systole in a way similar to that seen with mitral regurgitation (Fig. 18).

Proper timing of the left parasternal impulse can therefore provide valuable information regarding the etiology of the left parasternal lift. An early systolic lift with active rocking motion suggests right ventricular volume overload, a midsystolic gentle heave suggests right ventricular pressure overload or anterior wall dyskinesia, and a late systolic lift is indicative of either significant mitral regurgitation or myocardial aneurysm.

In our experience, precordial palpation has been a useful tool in differentiating constrictive pericarditis from the clinically similar but prognostically different, restrictive cardiomyopathy. Several decades ago, Wenckebach noted that in constrictive pericarditis the precordial movement is characterized by systolic retraction (negative wave) of the precordium. Our experience as well as that of others[8] supports this observation (Fig. 19) only with rare exceptions. By contrast, patients with cardiomyopathy exhibit systolic outward movement, rather than retraction in the left parasternal and apical regions (Fig. 20). The disparity is probably due to the fact that in constrictive pericarditis, the heart, which is usually normal in volume, is restricted by a noncompliant container. As the cardiac volume decreases in systole, retraction is noted in the precordium. With cardiomyopathy, the heart is usually dilated and its movements in the chest

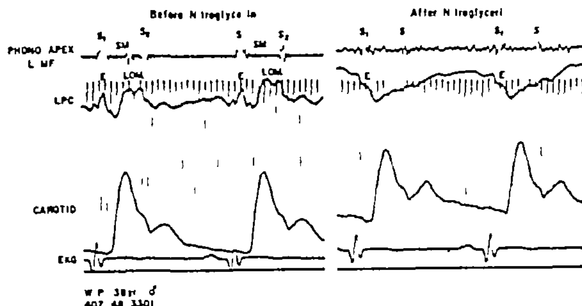


Fig. 18. Recordings from patient ith angina t rest due to proximal occlusion of the anterior descending branch of the left oronary artery. *Tracings of the left* ere obtained during hest pain, the left parasternal cardiogram is characterized by lat out ard movement signifying anterior wall dyskinesia. *Tracings to the right* were obtained after the angina ttack had been aborted with nitrogly erin, the left parasternal cardiogram shows normal e pattern.

are not restricted. A positive (outward) palpable cardiac impulse is therefore the rule particularly when the patient is asked to turn on his left side.

It is apparent from the previous discussion that the proper timing of the apical and left parasternal events perceived by palpation is crucial for the proper interpretation of the significance of these events. If a portable instrument should become available for the display of the ECG on a small scope upon contact with the chest wall, proper timing of palpable events would become readily accomplished and the art of precordial palpation could be revived as a useful clinical tool requiring only moderate training and skill.

To the experienced clinician, in addition to examining the apical and left parasternal impulses, precordial palpation provides valuable information regarding other precordial pulsations, accentuated cardiac sounds, and palpable murmurs. It continues to be a useful and challenging art in the clinical evaluation of cardiac disease.

Summary

The value and limitations of precordial palpation have been reviewed in the light of recent information. A markedly enlarged heart in the absence of significant increase in volume load signifies poor myocardial function. It is often difficult to differentiate a fourth heart sound from similar auscultatory phenomena, but a palpable presystolic kick is a reliable clinical clue to an elevated left ventricular end-diastolic pressure. A hyperkinetic apical impulse is seen in slim anxious patients, those with hyperkinetic states, and typically those with left ventricular volume overload. However a sustained systolic apical impulse need not necessarily mean increased pressure load on the left ventricle, as it could be encountered with combined volume and pressure load and in patients with markedly dilated left ventricle. A bifid systolic apical impulse has little significance. A trifid impulse (one presystolic and double systolic waves) is most often seen in idiopathic hyperkinetic subaortic stenosis.

The left parasternal impulse is normally characterized by a brief gentle early systolic lift followed by systolic retraction. A rocking movement with a lift starting in diastole and peaking in early systole is typical of right ventricular volume overload. A midsystolic gentle heave is seen in patients with decreased anteroposterior chest diameter in those with right ventricular pressure

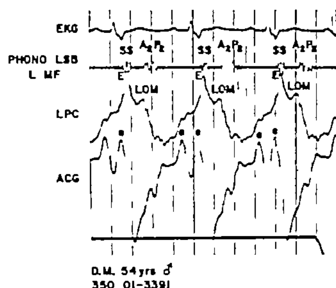


Fig. 17 Tracings from patient with left ventricular anterior wall dyskinesia due to prior myocardial infarction. The apexcardiogram shows a prominent presystolic wav signify ing high left ventricular end-diastolic pressure, but otherwise is normal. Note that while the apical impulse recedes w y from the chest wall during the latter part of systole, the left parasternal area shows a sustained outward movement signifying an anterior myocardial aneurysm.

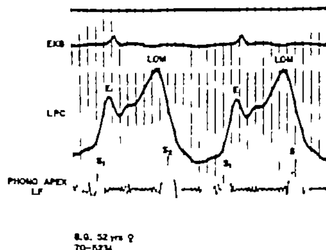


Fig. 18. Recordings from patient with large posterior myocardial aneurysm. Note that the left parasternal cardiogram shows prominent late outward movement similar to that seen in patients with sev re mitral regurgitation or anterior aneurysms. The whole heart seems to be pushed forward by the xpanding aneurysmal sac during systole.

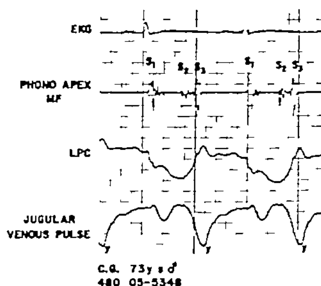


Fig. 19. ECG, phono, LPC, and jugular enous pulse tracing from a patient with constrictive pericarditis. Note that, i addition to the typical phonocardiographic and enous w patterns, the left parasternal cardiogram show a negativ wave that reaches its maximum after the second heart sound and is followed by the rapid filling diastolic wave.

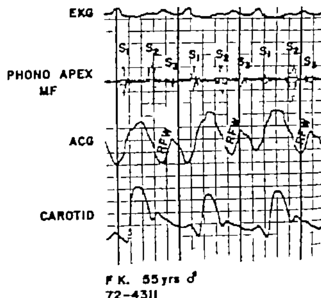


Fig. 20. Recordings from patient with restrictive cardiomyopathy due to amyloid heart disease. The apexcardiogram shows systolic outward movement and diastolic outward movement corresponding to the rapid filling phase. The pattern could be recorded from all over the precordium.

overloaded, and occasionally in those with anterior wall dyskinesia.

A late systolic lift is encountered typically in patients with mitral regurgitation and also with myocardial aneurysm. An example of the value of careful precordial palpation is in differentiating mitral regurgitation from aorti stenosis when the auscultatory findings are often indistinguishable. Mitral regurgitation gives a hyperkinetic apical impulse and a late systolic left parasternal lift, whereas aortic stenosis gives a sustained apical impulse and a gentle systolic retraction in the left parasternal area.

Also precordial palpation helps to differentiate

constrictive pericarditis from restrictive cardiomyopathy. The first leads to systolic precordial retraction while the latter produces a palpable systolic outward movement.

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Fundamentals of clinical cardiology

Radionuclide assessment of regional myocardial perfusion with thallium 201

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The marked prevalence and alarming natural history of coronary atherosclerosis make it imperative that a thorough evaluation of the coronary circulation be obtained in patients with known or suspected ischemic heart disease. In addition, an assessment of regional myocardial perfusion is important in the evaluation of the medical and surgical management of patients with ischemic heart disease. The coronary arteriogram provides anatomic information of the site(s) and degree of coronary arterial narrowing. However it does not provide functional information regarding regional myocardial flow at the capillary level; this information can be obtained with the use of radionuclides and a scintillation camera. Furthermore this technique is noninvasive and safe.

Radionuclide indicators available for assessment of regional myocardial perfusion include [illegible] particulate indicators, and diffusible inert gases ([illegible]Xe). The latter two indicators require cardiac catheterization and will not be discussed in this review. The following discussion will be restricted to potassium analogues, with major emphasis on thallium-201 ([illegible]Tl).

The approach of regional myocardial perfusion imaging with radioactive potassium or one of its analogues involves the intravenous injection of the radionuclide which is initially distributed to and concentrated by cardiac muscle. The myocardial accumulation of radiopotassium and rubidium was first demonstrated by Love and colleagues in 1954. Carr and associates[illegible] suggested the potential clinical application of this observation to imaging of the myocardium. They demonstrated[illegible] that significant radioactivity could be detected and imaged in the normal myocardium using rubidium-86 and cesium 131, and that following experimental coronary ligation the zones of decreased or absent radioactivity ("cold spots") could be visualized on the myocardial scan. Subsequently newer radionuclides have been developed, including potassium-43, cesium-129, rubidium-81 and thallium 201. While none of these tracers possess ideal physical and biological properties, thallium 201 appears to be the best of the currently available cationic tracers for myocardial perfusion imaging.

Physical and biologic properties of 201 thallium

Thallium-201 has a physical half life of 73 hours. While this provides and adquate shelf life, a longer time is required between sequential studies in the same patient. ^{201}Tl decays by electron capture, emitting a small yield of gamma rays (135 to 167 keV). In addition the daughter nuclide 201 mercury emits x rays with an energy of 65 to 82 keV; these x rays occur in 9[illegible] per cent of ^{201}Tl disintegrations. Although the energy spectrum of this radionuclide is less than optimal, ^{201}Tl can be effectively imaged with a scintillation camera. ^{201}Tl concentration in the blood decays exponentially with a half time of less than 30 seconds. In comparison with other cationic tracers, ^{201}Tl has a greater heart/blood and heart/

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liver ratio of activity The concentration of ²⁰¹Tl initially in the myocardium is between 2 and 5 per cent of the administered dose This myocardial concentration of tracer at any particular time after injection is influenced by the rate of turn over of the intracellular pool of these tracers in the myocardium. The myocardial half life of thallium is longer than that of potassium therefore myocardial imaging may be performed at least up to one hour after administration of ²⁰¹Tl and still reflect myocardial perfusion at the time of administration.

The initial distribution of ²⁰¹Tl in the myocardium is dependent on both coronary blood flow and cellular extraction. Strauss and associates compared the regional distribution of ²⁰¹Tl with that of radioactive microspheres (administered into the left atrium of dogs) as an indicator of blood flow and demonstrated excellent correlations under conditions of normal flow and partial and total coronary artery occlusion. These data suggest that the major determinant of ²⁰¹Tl distribution is blood flow Myocardial extraction of ²⁰¹Tl is dependent on an active transport mechanism involving the sodium-potassium membrane ATPase system. Extraction efficiency by the heart approximates 85 to 90 per cent. This may be reduced by hypoxia and acidosis, the effects of digitalis, propranolol, and insulin on ²⁰¹Tl extraction are conflicting.

Normal ²⁰¹Tl scan (Fig 1)

The appearance of the normal myocardial perfusion image after intravenous injection of ²⁰¹Tl at rest and exercise has been described by Cook and co-workers. At rest, the only portion of the heart normally visualized is left ventricular myocardium the right ventricular myocardium is not visualized, due to its thinner wall and lower blood supply When injection of ²⁰¹Tl occurs at the time of maximal exercise stress, lung, hepatic, and splanchnic activity diminish, and the right ventricular myocardium is visible on the scintigram, best seen in the 45 degree left anterior oblique view

In the anterior view the anterolateral wall, apex, and inferior wall of the left ventricle can be visualized. The apex frequently has less activity than the remainder of the myocardium, due to anatomic thinning in this zone. In the 45 degree left anterior oblique view the septum, posterolateral and inferior walls are detected if the heart has a vertical position in the chest, the apex makes up the inferior border In the left lateral view the anterior wall, apex, inferior and posterior walls are identified.

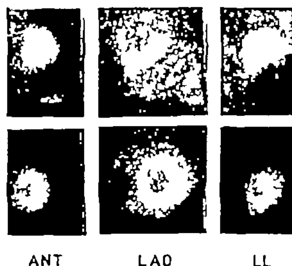


Fig 1 Normal thallium-201 myocardial perfusion scintigram at rest *(upper panels)* and exercise *(lower panels)* in patient with normal coronary arteries on selective coronary arteriography *ANT* = anterior view *LAO* = left anterior oblique view *LL* = left lateral view

It has been suggested that there are physiologic areas of decreased perfusion in the normal myocardium and therefore, that if lesions are to be considered significant, their radioactivity must vary by more than 20 per cent from adjacent areas.

Myocardial infarction

The major application of the assessment of regional myocardial perfusion with ²⁰¹Tl has been in patients with known or suspected ischemic heart disease. When myocardial imaging is performed at rest, ²⁰¹Tl is injected intravenously with the patient standing, after a 12 hour fast, in order to decrease hepatic and splanchnic blood flow Regions of recent or old myocardial infarction appear as areas of reduced tracer uptake at rest which do not change with exercise (vide infra) (Fig. 2) This is due to reduced blood flow to the infarct area and a reduction in myocardial cellular mass. The sensitivity of the procedure for acute myocardial infarction is approximately 80 per cent. The frequency of positive scintigrams was significantly higher in patients studied within 24 hours after onset than in those studied later Repeat scintigrams in the

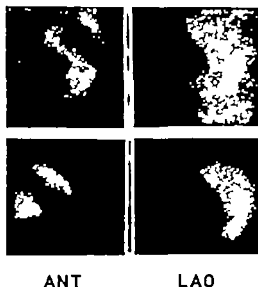


Fig 2. Myocardial infarction showing rest defect. Thallium-201 myocardial perfusion scintigram in patient with 100 per cent obstruction of the left anterior descending and right coronary arteries. There is a focal defect in olving the septum and inferior wall of the left entricle at rest *(upper panels)* which is unchanged after exercise *(lower panels)*, consistent with myocardial infarction without ischemia.

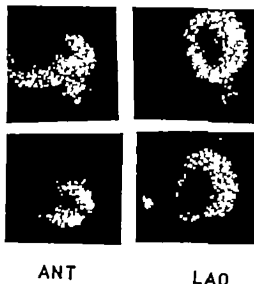


Fig. 3. M ocardial ischemia with exercise-induced defect. A patient with myocardial ischemia and 95 per cent stenosis of the left anterior descending coronary artery. The thallium-201 scintigram is normal at rest *(upper panel)*. After exercise there is perfusion defect involving the pex and lower portion of the septum *(LAO iew)*.

same patient demonstrated a reduction in the size of the defect with time these observations suggest that during the acute stage of myocardial infarction the perfusion defect is due to a combination of myocardial necrosis, ischemia, and peri-infarction edema. It is important to note that Tl perfusion scintigraphy does not differentiate between old and new infarction. Ancillary information and the use of infarct avid agents such as 99m technetium (99m Tc) pyrophosphate aid in this distinction. Abnormal resting Tl scintigrams have also been reported in patients with unstable angina pectoris, and in patients with coronary spasm.

Defects in the Tl scintigram at rest appear to be more sensitive than the 12 lead electrocardiogram or the ventriculogram. Myocardial perfusion defects accurately localize the site of transmural infarction However the ability of the procedure to estimate the size of the infarct is presently limited dual radionuclide studies with Tl combined with infarct avid agents such as 99m Tc pyrophosphate may improve results.

There are additional limitations with Tl rest imaging for myocardial infarction Lesions less than 2.5 cm. cannot usually be detected, inferior and posterior infarcts are more difficult to visualize than anterior infarcts. Furthermore, thallium myocardial perfusion imaging is unable to detect lesions that are limited to the subendocardium.

Myocardial ischemia

When patients with angina pectoris without myocardial infarction are imaged at rest, regional perfusion is generally normal. In the resting nonischemic state, viable myocardial regions supplied by stenotic coronary arteries are usually adequately perfused in either an antegrade or retrograde fashion. Both resting coronary blood flow and regional distribution were normal in animals despite coronary stenosis of 85 per cent in diameter However the ability to increase coronary flow in response to stress became progressively abnormal with coronary stenosis exceeding 45 per cent. Therefore, by combining a stress with the imaging procedure, one can image transiently ischemic myocardium which appears as a region of decreased radioactivity compared to a separate rest image (Fig. 3) Patients are exercised on a treadmill or bicycle until limited by angina, dyspnea, significant arrhythmias, or the attainment of 85 per cent of the maximum predicted heart rate. Tl is then injected intravenously and the patient continues to exercise for 45 to 60 seconds

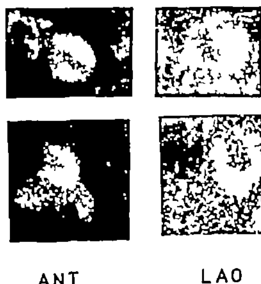


Fig. 4. Myocardial ischemia with defect at exercise disappearing 4 hours later. Thallium-201 myocardial perfusion scintigram 10 minutes after exercise *(upper panel)* and 4 hours later *(lower panel)*. The decreased tracer concentration 10 minutes after exercise is not present 4 hours later indicative of myocardial ischemia. Coronary arteriography revealed 90 per cent obstruction of the left anterior descending coronary artery.

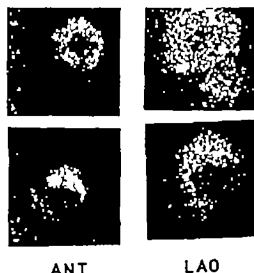


Fig. 5. Myocardial infarction with additional ischemia. A patient with triple vessel coronary disease and a previous myocardial infarction. On the rest injected thallium scintigram *(upper panel)*, there is decreased tracer concentration in the inferior wall seen best in the *LAO* view. With injection at peak exercise *(lower panel)*, the inferior defect becomes more marked and there is decreased perfusion of the apex *(Ant view)*, septum and posterolateral walls *(LAO view)*, consistent with myocardial infarction and ischemia.

following injection. The ^{201}Tl is rapidly cleared from the blood and distributed within the ventricular myocardium, the proportion distributed within the left ventricular myocardium remains essentially unchanged for at least one hour after injection and, therefore, reflects the physiological state at the time of the radionuclide injection. Thus, imaging from 10 to 60 minutes after injection reflects the distribution of the radioactive cation at the time of stress, even though the patient has returned to the resting state. Mechanisms responsible for the abnormal ^{201}Tl uptake under stress include more ^{201}Tl being delivered to normal myocardium in comparison to that in the myocardium distal to the critical stenosis, and decreased extraction efficiency under conditions of hypoxia and acidosis. Recent reports indicate that imaging repeated 4 hours after exercise demonstrate resolution of exercise-induced myocardial defects, thereby obviating the need for a separate rest study (Fig. 4). Rest defects associated with an increased perfusion defect with exercise are consistent with both previous infarction and myocardial ischemia (Fig. 5).

Studies evaluating patients undergoing rest and exercise ^{201}Tl imaging have demonstrated a sensitivity of approximately 75 to 80 per cent in detecting significant coronary artery disease. Our current results confirm these findings. This sensitivity is higher than that reported with either the resting or exercise ECG. When the results of rest and exercise ^{201}Tl myocardial perfusion scintigrams are combined with the results of the rest and exercise ECG, the sensitivity increases to approximately 90 per cent.

^{201}Tl imaging is particular helpful in patients with single vessel coronary artery disease, those with abnormal resting ECG's and those with exercise ECG's which are difficult to interpret because of conduction abnormal abnormalities or ventricular arrhythmias.

Myocardial imaging with ^{201}Tl is currently generally a qualitative study dependent on the demonstration of relative differences in radionuclide uptake. In the presence of global ischemia due to severe proximal triple vessel disease or bilateral coronary ostial stenosis, a normal homogenous appearing scan would be evident. Quantification of the ^{201}Tl scintigram has demonstrated a reduction in total myocardial activity. False-negative studies may also occur in single vessel

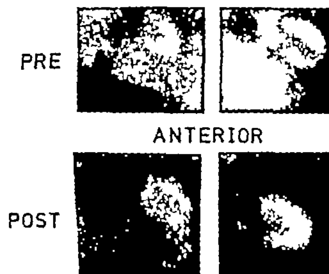


Fig. 6. Effects of coronary artery bypass graft surgery. Preoperative *(upper panels)* and postoperative *(lower panels)* thallium-201 scintigrams at rest and exercise *(anterior view)*. The resting scintigrams are normal. The perfusion defect in the exercise scintigram preoperatively is not present after coronary bypass surgery. Preoperative coronary arteriography revealed 95 per cent stenosis of the left anterior descending coronary artery. Coronary arteriography 3 months postoperatively revealed a patent graft to the left anterior descending coronary artery.

disease involving either the right or the circumflex coronary artery. In addition, in the presence of a large myocardial infarction, an exercise defect may be difficult to demonstrate.

We have found the specificity of ²⁰¹Tl exercise scintigraphy to be 90 per cent,[8] confirming recent reports by Ritchie and associates[11] and by Botvinick and colleagues. However since these results were obtained from selected populations, more experience is necessary before the specificity of ²⁰¹Tl scintigraphy is definitively established.

An extension of the use of myocardial perfusion imaging has been employed in the evaluation of patients who have had coronary bypass surgery. The post surgical studies by Zaret and co-workers[4] using potassium 43 have been confirmed recently with Tl. Comparison of pre- and postoperative rest and exercise scintigrams have provided information regarding graft patency, status of the distal native circulation and perioperative infarction (Fig. 6).

An additional application of the exercise ²⁰¹Tl myocardial perfusion scintigram has been advocated in asymptomatic patients or patients with atypical chest pain and ST segment depression 1 mm. or greater on exercise testing. The finding of a perfusion defect on the exercise ²⁰¹Tl scintigram would suggest coronary stenosis, whereas a normal exercise ²⁰¹Tl scintigram would suggest that the exercise ECG was not indicative of hemodynamically significant coronary atherosclerosis.

Non-coronary cardiac disease

²⁰¹Tl perfusion imaging has also been used to evaluate patients without coronary disease. Patients with tetralogy of Fallot have been differentiated from patients with single ventricle by the appearance of the septum on the scintigram.[13] An increase in septal thickness relative to the left ventricular free wall with a ²⁰¹Tl perfusion scintigram has been demonstrated in idiopathic hypertrophic subaortic stenosis.[14] Furthermore patients with the obstructive form of the disease have a thicker basal posterior free wall than patients with the nonobstructive form of this disease. In idiopathic congestive cardiomyopathy thallium uptake is generally uniform whereas in ischemic cardiomyopathy focal defects in uptake are apparent. While left ventricular dilatation was found in both conditions, right ventricular dilatation was more common in idiopathic congestive cardiomyopathy. Cardiomyopathy due to infiltrative systemic disease such as sarcoidosis[15] are associated with focal decreases in ²⁰¹Tl concentration. The scintigram is not specific, however and coronary artery disease must be differentiated on clinical grounds. Finally thallium perfusion imaging has been reported to be a useful technique for the diagnosis of right ventricular (RV) hypertrophy.[16] On low contrast ²⁰¹Tl scintigrams at rest, Cohen and colleagues[16] visualized the RV in all patients with RV hypertrophy; in addition there was apparent thickness of the RV free wall. This technique was more sensitive than the ECG.

Future developments

While ²⁰¹Tl is the best of the currently available potassium analogues, the optimal gamma emitting radioactive potassium analogue has not become available. It is anticipated that the future will see the development of more optimal radionuclides as well as improvements in imaging techniques and development of quantitative approaches to myocardial imaging with improved computer data processing. Methods for accurately sizing acute myocardial infarction with or

without the concomitant use of infarct avid agents, and for providing sequential follow up information are needed. Finally the use of positron-emitting potassium analogues and the positron camera promise improved spatial resolution in perfusion scintigraphy and the potential for three-dimensional reconstruction

Conclusions

In conclusion, assessment of regional myocardial perfusion with ²⁰¹Tl rest and exercise provides useful information employing a technique that is non invasive and safe. It can be performed on acutely ill patients and can be repeated for re-evaluation. The reproducibility of repeat ²⁰¹Tl myocardial imaging' enables this diagnostic study to be employed in longitudinal follow up studies. Since the myocardial perfusion scintigram provides functional information regarding regional tissue perfusion whereas the coronary arteriogram provides anatomic information these two procedures are complementary and not competitive.

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Appraisal and reappraisal of cardiac therapy

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Aprindine

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For many years clinicians have been limited by the availability of efficacious antiarrhythmic drugs. A major lack has been of agents that are effective by both the oral and parenteral routes, that have a sustained time course of action against a variety of arrhythmias, and a low toxicity A recently developed drug purported to meet these requirements is aprindine, which was developed in Belgium (Fiboran, A. E. Christiaens) Its chemical structure is shown in Fig 1 Aprindine possesses some structural similarities to procainamide, lidocaine and propranolol in that all four agents consist of an aromatic residue, an intermediate chain and an amino group with two ethyl groups attached. All four exert local anesthetic effects on cardiac transmembrane action potentials. Aprindine is now available in the United States as Fibocil (Eli Lilly & Co) for clinical investigation. It has been the subject of a symposium and the current literature has been recently reviewed by Zipes and Troup

1 Clinical use

In man, aprindine is effective against ventricular arrhythmias of diverse etiologies. Kesteloot and colleagues found aprindine effective in treating ventricular premature depolarizations (VPDs) and ventricular tachycardia (VT) Aprindine was administered intravenously in doses of 20 mg. every 2 minutes until a therapeutic effect was observed or until a total dose of 140 mg. was administered. In some instances 25 mg. of aprindine was administered every 2 minutes (a total dose of 150 mg.) In others, 250 mg. was given more slowly by infusion. Aprindine was administered orally to selected patients as a loading dose of 200 to 400 mg. on day 1 followed by 100 to 300 mg. on day 2 and then by a 100 to 150 mg. maintenance dose thereafter Of 11 patients, aprindine completely abolished VPDs in eight, decreased VPDs by 50 to 75 per cent in two and had no effect in one.

In the same study aprindine was administered to four patients with VT The arrhythmia had occurred for "hours to weeks" and was diagnosed on the basis of the repeated occurrence of at least three sequential ventricular complexes at a rate of > 100/minute. In three of the four cases, intravenous administration of 100 to 150 mg. of aprindine was associated with complete abolition of VT and in the remaining case the incidence of VT was reduced by 80 per cent. In four patients with idioventricular tachycardia, two were completely cured of their arrhythmia by aprindine and two were refractory Of the two aprindine-resistant cases, one did not respond to intravenous aprindine, 200 mg., or to any other available antiarrhythmic agents.

Van Durme and co-workers[4] studied 129 patients with stable VPDs associated with coronary heart disease (64 per cent) valvular heart disease (11 per cent) hypertension (3 per cent) cardiomyopathy (3 per cent) non-cardiac causes (4 per cent) and unknown causes (15 per cent). Data were obtained by scanning electrocardiograms obtained for 5 minutes three times a day or by continuous monitoring for an unspecified period of time using a Holter system. All other antiarrhythmic therapy was stopped at least 3 days prior to aprindine administration. Complete suppression of VPDs was observed in 67 per cent of the cases and 50 per cent suppression of VPDs with elimination of repetitive/multifocal VPDs was observed in 14 per cent. No effect was noted in 19 per cent. More recently Fasola and associates, in a well-controlled study evaluated th

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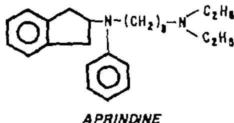


Fig. 1 N-[3-(diethylamino)propyl]-N-phenyl 2-indanamine.

effect of aprindine on recurrent VT and fibrillation (VF) in 23 patients who had not responded well to various combinations of procainamide, quinidine, lidocaine, propranolol, or diphenylhydantoin. Arrhythmias before administration of aprindine were evaluated by continuous monitoring of the electrocardiogram and/or continuous Holter monitoring. Holter monitoring before aprindine averaged 108 hours for each patient. Following administration of aprindine, Holter monitoring was continued for an average of greater than 900 hours/patient. Aprindine, administered orally was given as an initial 200 mg. dose, followed by 100 mg. 1 hour later and again 4 to 10 hours later. On day 2 of oral aprindine therapy a total dose of 300 mg was administered and on day 3, 400 mg. was given. On subsequent days the dose was adjusted for each patient to obtain the maximal antiarrhythmic effect with minimal side effects. Of 13 patients with recurrent VT/VF 11 remained asymptomatic during chronic aprindine therapy. Five deaths occurred in this group apparently unrelated to either cardiac arrhythmias or to aprindine administration. In 10 patients with recurrent VT nine remained asymptomatic during chronic aprindine therapy. The effectiveness of aprindine in the treatment of ventricular arrhythmias as been demonstrated by others.

Aprindine has also been used in the treatment of supraventricular arrhythmias, although with somewhat less success than with ventricular arrhythmias. Kesteloot found that aprindine was effective in the treatment of atrial fibrillation of recent onset (four cases) but ineffective in chronic atrial fibrillation associated with heart failure. Treatment of atrial flutter with aprindine was unsuccessful (five of six cases). Although the flutter rate decreased the ventricular response to flutter increased. Two of three cases of paroxysmal atrial tachycardia responded favorably to aprindine (150 mg., intravenously) chronic atrial tachycardia was successfully treated with aprindine in three of five cases. Two cases of Wolff Parkinson White syndrome with paroxysmal tachycardia showed improvement following aprindine administration. Similar effects of aprindine in the Wolff Parkinson White syndrome have been described. Breithardt and colleagues found that aprindine administered orally over 1 to 18 months reduced the frequency of APDs in four of four patients. Bollen and Enderle reported that aprindine (100 to 300 mg., total dose) completely abolished APDs in 12 of 16 cases and reduced the incidence of APDs by 50 per cent in two of 16. Paroxysmal atrial tachycardia responded to aprindine (100 to 400 mg., total dose) in a similar manner—ten of 12 cases were converted to sinus rhythm. Atrial flutter and fibrillation appeared to respond less favorably. Four of eight cases of atrial fibrillation showed complete reversion to sinus rhythm and four were refractory to aprindine. Of two cases of atrial flutter one returned to sinus rhythm.

Zipes and co-workers studied 10 patients with supraventricular tachycardia who had failed to respond to conventional antiarrhythmic drugs. Nine of these patients had the Wolff Parkinson White syndrome. Before aprindine was administered, supraventricular tachycardia (SVT) was initiated in eight of 10 patients using properly timed stimuli. Aprindine was then administered according to the following schedule: 200 mg (initial dose) followed by two additional doses of 100 mg., each, on day 2 300 mg., and on day 3, 200 mg. of aprindine was administered. On subsequent days the dose was individualized according to the observed response. Following aprindine, paroxysmal SVT could not be elicited in four patients. In the remaining four administration of aprindine did not prevent the induction of SVT. In this latter group aprindine reduced the ease with which SVT could be induced (two patients) or facilitated it (two patients).

In the group of four patients in whom SVT could be initiated during treatment with aprindine, the rate of the tachycardia was lower after administration of aprindine.

Effects on experimental arrhythmias. In dogs subjected to two-stage ligation of the left anterior descending coronary artery aprindine administered orally[11] or intravenously[12] reduced the frequency of VPDs. However VF occurring in dogs after single stage coronary artery occlusion and release responded less well to aprindine. Also,

pretreatment with aprindine (5 mg./Kg.) exerted no protective effect against VF associated with complete occlusion[13] or complete occlusion and release in dogs. In pigs subjected to a 75 per cent decrease in flow through the left anterior descending coronary artery aprindine 2.8 mg./Kg intravenously decreased the mortality rate due to fibrillation from five of 22 animals in a control group, to one of 23 animals in the aprindine-treated group.[14]

Aprindine 0.5 to 2.0 mg./Kg., intravenously did not prevent the occurrence in cats of ventricular arrhythmias induced by rapid intravenous administration of epinephrine 30 to 50 μg/Kg

Aprindine is effective against digitalis-induced arrhythmias in experimental animals. Aprindine, 4.4 mg. administered intraduodenally as a single dose was effective against ouabain induced ventricular arrhythmias in dogs. Intravenous administration of aprindine 2.9 mg./Kg suppressed ouabain induced arrhythmias in dogs in 14 of 14 experiments. Similar effects of aprindine on ouabain induced arrhythmias have been demonstrated by others in the dog, guinea pig, and cat.[11]

2. Pharmacokinetics

Aprindine is effective as an antiarrhythmic when administered orally or intravenously. It is 85 to 95 per cent protein bound. In dogs and man it is metabolized in the liver by aromatic hydroxylation and N-dealkylation and the major portion of these metabolites undergoes glucuronidation in the liver. At least one metabolite N-desethyl aprindine possesses some antiarrhythmic activity. In man, approximately 40 per cent[15] to 85 per cent of a given dose of aprindine is eliminated in the urine, and as much as 35 per cent is eliminated in the feces.[16] Elimination of aprindine has been explained using a two compartment model.[2] The early rapid phase has a $t_{½}$ of 0.5 to 2.7 hours and the later slower phase has a $t_{½}$ of 12.5 to 66 hours.

Effective plasma levels of aprindine have been reported to range between 0.32 to 6.6 μg/ml. (1 to 3 μg/ml., mean)[2]

3. Toxicity

Side effects of aprindine are reportedly dose-related and appear to be manifest mainly through the CNS and less frequently through the gastrointestinal system. These toxic signs include fine tremor and nervousness (most common) intention tremor dizziness and ataxia. The following have also been reported, although less frequently fatigue, headache, nausea and vomiting and, rarely hallucinations and seizures. These untoward effects seldom occur at aprindine plasma levels of ≤ 1 μg/ml. and occur with increasing frequency when plasma levels exceed 2 μg/ml. For the most part, therapeutic effects of aprindine can be attained at plasma levels (i.e., between 1 and 2 μg/ml.) below those which induce toxicity of sufficient magnitude to require cessation of aprindine therapy. Agranulocytosis[17, 18] and cholestatic jaundice[7] have also been reported to occur in association with aprindine therapy. Both of these side effects are thought to be idiosyncratic and unrelated to the dose of aprindine. Of eight patients with agranulocytosis, two died as a result of this side effect and the remainder showed signs of recovery 1 to 4 weeks after cessation of aprindine.[17] Of five patients with hepatotoxicity during treatment with aprindine,[19] two developed severe cholestatic jaundice within 2 to 3 weeks after beginning aprindine, three showed less severe signs. Following cessation of aprindine therapy normal liver function returned. Three of these same patients submitted to subsequent challenges with aprindine and showed signs of abnormal liver chemistries.

The incidence of agranulocytosis in Europe is on the order of one in several thousand, while in the United States it is currently three in 400 cases (Dr. J. G. Armstrong, personal communication). Additional data must be collected in the United States to determine whether the incidence is related to aprindine or to some other factor.

4. Hemodynamic and autonomic effects of aprindine

Aprindine exerts a negative inotropic effect on isolated cat papillary muscle.[23] Aprindine, 2.5 to 5.0 μg/ml., decreases peak developed tension and the rate of tension development. Results obtained from intact animals have varied due in part, to species differences and variation in technique. Aprindine has been reported to decrease myocardial contractility slightly in conscious dogs in a dose-dependent manner unaccompanied by significant changes in LVEDP or LVSP.[24] Effects of aprindine on cardiac contractility in anesthetized dogs and pigs[14, 27] have been reported as slight at low doses (0.3 to 4 mg./Kg). In open-chested

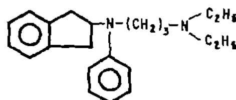


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dogs[11] under halothane/N O anesthesia, significant decreases in "LVP" were observed at aprindine doses of ≥ 6 mg./Kg., while LV dp/dt was decreased at aprindine 4 mg./Kg. Stroke volume was decreased at relatively high aprindine doses (6 to 8 mg./Kg.) Studies of pentobarbital-anesthetized pigs showed that aprindine ≤ 7.8 mg./Kg., had little effect on LVEDP while induring a marked dose-dependent decrease in LV dp/dt. Cardiac output is decreased by relatively high doses of aprindine (3.8 to 6 mg./Kg.) in open chested dogs[11] and in pigs.[27] Studies in humans have shown a similar effect of aprindine on LV dp/dt.[28] In both man and animals, aprindine has little effect on arterial blood pressure [27, 28, 29] except at high doses, i.e., 10 mg./Kg. in the dog.

Aprindine is reported to have little effect on autonomic responses mediated by adrenergic or cholinergic receptors. Georges and colleagues showed that intravenous aprindine, 0.5 to 3.0 mg./Kg., did not prevent the increase in blood pressure induced by epinephrine or norepinephrine, the tachycardia resulting from injection of isoproterenol, on the hypotension and bradycardia induced by intravenous acetylcholine Elharrar and associates showed that the effects of aprindine can occur in the presence of adrenergic and cholinergic blockade.

5 Effects on cardiac impulse initiation and conduction

Aprindine slows conduction in all cardiac tissues. In experimental animals, aprindine has been variably reported to decrease[11] or increase[27] sinus rate Aprindine slows intraatrial conduction in man and experimental animals. In both man and animals, aprindine slows conduction through the atrioventricular (AV) node through an increase in A H and H V intervals. Effective and functional refractory periods of the A V node in man[14] and animals are increased and intraventricular conduction is slowed. It is of interest that the effects of aprindine on the P R interval and QRS duration have been reported to be antagonized partially by adrenergic stimulation (See Hemodynamic effects of aprindine above) Aprindine has also been found to block conduction through pathways involved in the Wolff Parkinson-White syndrome

6 Cellular electrophysiological effects of aprindine

Microelectrode studies of isolated cardia[c] preparations indicate that aprindine exerts loc[al] anesthetic effects. Aprindine 0.5 to 5 μg/m[l] decreases action potential amplitude and maxi[mum] rate of rise of phase 0 depolarization ($\dot{V}_{max}$) of bovine Purkinje fibers in a concentration[-] dependent manner[15] Steinberg and Greenspan showed that aprindine (approximately 1 μg/ml) significantly decreased $\dot{V}_{max}$ of isolated canin[e] Purkinje fibers while exerting no significant effec[t] on maximum diastolic potential. Aprindin[e] decreased Purkinje fiber action potential dura[-] tion by decreasing the time course of full repolar[-] ization and by decreasing the plateau height suggesting that aprindine may alter potassium and other ionic currents (e.g., Ca) operating i[n] the range of plateau potentials. Verdonck and co-workers[15] showed that, for bovine Purkinje fibers, ($[K]_o$ = 5.4 mM.) with a total action potential duration of approximately 600 msec. aprindine 1 microgram per milliliter decreased total duration approximately 22 per cent. Steinberg and Greenspan[16] studied canine Purkinje fibers ($[K]_o$ = 4 mM.) and showed that aprindine, 1 microgram per milliliter decreased action potential duration (measured to 95 per cent repolarization) to 13 per cent, compared to control. This slight difference in effect of aprindine may be due to species variability to effects of different $[K]_o$, to temperature, or to different rates of stimulation.

Verdonck and colleagues[15] and Carmeliet and Verdonck[37] suggest that the effect of aprindine is not due to an effect on gK since aprindine had no effect on K-efflux at a $[K]_o$ of 0 or 5.4 mM. They further suggest that the "stabilizing" effect of aprindine may be due to a decrease in membrane permeability to Na rather than an increase in permeability to K

Aprindine may exert a different effect on the action potential of ventricular myocardium than on Purkinje fibers. Verdonck and associates[15] compared the effects of aprindine on bovine Purkinje fibers to those on guinea pig ventricular muscle. They found that aprindine had less effect on action potential duration of guinea pig ventricle than that of bovine Purkinje fiber The importance of this result depends upon the extent to which aprindine effects on ventricular myocar

dium from one species (guinea pig) can be compared to effects on Purkinje fibers from another (cow)

Consistent with the effect of aprindine on action potential duration is its action on effective refractory period (ERP) Aprindine decreases the ERP of bovine[11] and canine[*] Purkinje fibers. These effects of aprindine on isolated cardiac preparations occurred rapidly and, for therapeutic concentrations, appear to be readily reversible Higher aprindine levels took longer to reverse

Aprindine has been reported to decrease Purkinje fiber automaticity [13] Verdonck and colleagues,[13] studying bovine Purkinje fibers at an unspecified temperature at a $[K^+]_o$ = 5 4 mM found that normal automaticity (i.e that occurring at membrane potentials of approximately −90 mV) is decreased by aprindine 1 µg/ml. These authors also state (but do not show) that aprindine, 1 µg/mL, can completely reverse the effects of epinephrine 1 µg/ml. on normal phase 4 depolarization (which at least suggests that aprindine may possess β blocking properties). Further aprindine markedly decreased the slope of phase 4 depolarization of bovine Purkinje fiber when studied at a [K] of 1.35 mM In addition, fibers depolarized by a K free solution, aprindine, 2 µg/mL, induced a hyperpolarization from approximately −40 mV to −65 mV Steinberg and Greenspan[*] also state that aprindine decreased Purkinje fiber automaticity

Slow response action potentials initiated at relatively low levels of membrane potential (−40 to −60 mV) and having low upstroke velocities have been suggested to underlie certain types of cardiac arrhythmias. Carmeliet and Verdonck[*] have demonstrated a lack of effect of aprindine, 2 µg/mL on slow response action potentials recorded from cat papillary muscle superfused with a solution containing 27 mM K. Similarly a lack of effect of aprindine on slow responses induced in canine Purkinje fibers by KCl (22 mM) and isoproterenol has been reported in preliminary fashion by Elharrar and colleagues.[*] Transient depolarizations induced by acetylstrophanthidin were suppressed by aprindine Preliminary results of others, however [*] suggest that aprindine may alter abnormal slow response automaticity of cardiac tissues superfused with Na free, Ca rich solutions. In canine Purkinje fibers depressed by stretch hypoxia digitalis or catecholamines, aprindine decreased the slope of phase 4 depolarization associated with each of the interventions,[43] suggesting that aprindine may affect action potentials initiated at lower than normal membrane potentials. Further investigation is required to determine to what extent aprindine exerts effects on ionic currents underlying the slow response action potential.

Conclusions

Aprindine is a long acting antiarrhythmic agent effective when administered orally or intravenously in the treatment of ventricular arrhythmias of varying etiologies. It may be especially useful in the treatment of the Wolff Parkinson White syndrome. To a lesser extent, it may be useful in the treatment of atrial arrhythmias. Side effects can be minimized by careful titration of the dose of aprindine. If the frequency of such serious side effects as cholestatic jaundice and agranulocytosis remains low enough, aprindine should prove to be a useful addition to currently available antiarrhythmic drugs.

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Annotations

Respiratory viral infections and renal disease

The well-recognized clinical association between acute upper respiratory tract virus infections and acute nephritis, nephrotic syndrome, exacerbations of these diseases and Goodpasture syndrome, has never been satisfactorily explained. The association with influenza was reviewed by Thomson and MacAuley[1] after the 1918-19 influenza pandemic. Goodpasture description of the syndrome which bears his name was in association with the same influenza outbreak. Recurrent hemorrhagic nephritis has been clearly associated with influenza A infection, as has acute renal failure and Goodpasture's syndrome. Killed influenza vaccine has been reported to adversely affect pre-existing glomerular disease. A recent review of viral infections and renal disease, however makes only passing reference to causal relationship between acute respiratory virus infections and renal disease. Several potential pathogenic mechanisms by which respiratory viruses could cause renal pathology have been suggested. They are direct effect of the virus, intravascular coagulation, and the varieties of immunologically mediated tissue damage.

A direct cytopathic effect of virus is possible. Many respiratory viruses grow well and induce cytopathology in cultured renal cells. The myxoviruses, which include influenza and parainfluenza, have surface neuraminidase. This enzyme splits sialic acid from glycoproteins. Glomerular basement membranes are rich in such proteins and experimental administration of neuraminidase in mice has been shown to cause alteration of glomerular structure. However evidence for viremia or renal infection in all but the most overwhelming respiratory virus infections is lacking.

Disseminated intravascular coagulation has followed severe respiratory virus infections and been associated with catastrophic renal pathology. This may follow agglutination and destruction of platelets after absorption of virus to their surface. Immune complexes could also trigger the coagulation cascade as could hypoxia, acidosis, and non-specific tissue damage. Fibrin degradation products have recently been reported transiently in the urine of healthy normal adults who had suffered trivial upper respiratory tract infections. In this study complement (C) and IgG were also found simultaneously in the urine. It was suggested that transient immune-complex mediated glomerulitis had occurred.

Because of the well-documented experimental nephropathies caused by circulating antigen/antibody complexes and by antibody directed particularly against glomerular (GBM) but also tubular (TBM) basement membrane antigens, these immunologic entities are frequently sought in renal disease in man. The presence of anti-GBM antibodies, which may cross-react with lung basement membranes, is a definite requirement for the diagnosis of Goodpasture syndrome and has followed influenza A infection. Studies in animal models of non-lethal respiratory myxovirus infections have thrown some light on the other possible immunopathologic mechanisms.

Immune complexes of viral antigen and antibody have been regularly found in the lungs and frequently in glomeruli and on the TBM of rodents 2 to 12 days after non-lethal primary myxovirus infections. Gross histologic renal damage was not detected. The timing was identical to the urinary findings in man, referred to earlier. Since about one sixth of the total cardiac output goes through the kidney without an intervening reticulo-endothelial barrier it is not really surprising that immune complexes arising in the lung should frequently be deposited in the kidney. In animals pre-treated with cyclophosphamide, the lung and renal findings were greatly diminished. The presence of immune complexes in lung tissue was invariably associated with complement deposition (unpublished) and, between days 3 to 9, desquamation and necrosis of infected mucosal cells and destruction of bronchial basement membranes (BBM). Viral antigens were detected in mucosal cells, on the cell membranes, and on BBM. This could clearly lead to the generation of cross-reacting antibodies to cytoplasmic, cell membrane, and basement membrane antigens. In some animal studies there was late and sometimes progressive appearance of linear IgG staining of GBM and TBM. Elution studies to determine whether specific anti-basement membrane antibodies were present are not complete. In studies in mice there are some preliminary data that genetic make-up played a role in the incidence and severity of both lung and renal lesions[1] and that transient albuminuria occurred (unpublished). It is also noteworthy that granular glomerular IgG staining often persisted in mice after viral antigens from the infecting virus had disappeared. The antigen in these presumed immune complexes is not known but could be antigens from a different virus (e.g., chronic murine leukemia virus[11]) or other endogenous antigens. For the hypothesis which follows the most attractive antigen candidates would be derived from basement membrane or mucosal cells.

The findings in rodents suggest that the following immunopathological consequences could occur dependent, at least in part, on the genetic background and related immunologic responsiveness of the host and the character and severity of the respiratory virus infection.

1. Early (2 to 10 days) transient renal immune-complex deposition involving the respiratory virus antigens.

2. A later auto-immune response to damaged host bronchial mucosal cells and basement membrane antigens. Immune complex mediated damage with soluble circulating cellular or basement membrane antigens could occur as in the Heymann nephritis model. Alternatively or perhaps in addition, cross-reacting anti-GBM or anti-TBM disease could be produced.

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3. An uto-immune response after renal damage caused by 1 (bove) directed more precisely at renal antigens.

4. Acti ation of latent or chronic virus infection with classical immune-complex deposition in the kidney The viral antigens would not then be derived from the original respira tory virus.

If this postulated series of events were t occur then a sequence of completely different respiratory virus infections could exacerbate renal pathology induce chronicity or change the character of the original immunopathological damage. Furthermore, after recovery from the respiratory tract infection, antigens from the infecting virus may never be detected in the kidney

Since adults average 2 t 4 respiratory virus infections each year and children even more the pathological mechanisms suggested could describe the commonest pathways to acute, recurrent, and chronic renal disease in man. Most infections probably result in acut sub-clinical renal damage. Compre hensive and sophisticated nephrologic and immunologic stud ies in these common afflictions are both urgently needed and greatly handicapped by the technical lack of promptness and diagnostic precision in respiratory rus infections. It is prob-able that definitive studies must wait future clearly identi-fied respiratory irus epidemics. However preliminary data could be gathered from studies of patients with clinical, non-bacterial, upper respiratory tract infections.

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Of walking into the ocean

Patients with tight mitral al stenosis present interesting descriptions of their respira ry difficulties when they walk into the ocean to wad or swim As they w lk int deeper and deeper w ter and the ocean level rises higher and higher onto their bodies, they feel more and more congested or "full in their chest and become more and more dyspneic This state often develops before the w ter level reaches the lower ribs and certainly as the chest begins t be submerged. The dyspnea becomes so distressful that these patients cannot proceed into deeper w ter and are forced t retreat t the beach to restore comfort This xperience is repeatedly revealed in history taking among patients with mitral valve stenosis. The tighter the stenosis, the less w ter depth these patients are able to walk into. They of course, are unable to dive.

This phenomenon appears to me to be caused by the ater pressing symmetrically upon the superficial veins of the lower extremities and abdomen, squeezing blood rather rapidly into the lungs. Fairly large volumes of blood lodged in the superficial veins are readily squeezed centrally int the right trium, then into the right ventricle and finally into the vessels of the lungs since there are no valves in the veins or other obstruc-

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tions to interrupt blood flow into the lungs. The blood accumulates in the lungs more rapidly than it can flow through the stenotic mitral valve. Furthermore, in mitral valve stenosis, the pulmonary vessels are often tight (constricted) and/or thickened and less distensible than normally so that they are less compliant and thereby less able to accommodate the fairly rapid volume inflow from the systemic veins, thus stimulating the respiratory reflexes which are responsible for the dyspnea and respiratory discomfort and distress. It should be noted that this phenomenon is also true for patients with left ventricular congestive heart failure caused by any type of heart disease. Such consideration are not only thought provoking, but they are also important in management of such patients. Patients with mitral stenosis should be advised not to walk into the ocean, swim, or dive.

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New treatment for congestive heart failure

The recent discovery of the value of drug-induced vasodilatation in cardiac failure has already received extensive reviews. These authors, however, seem unaware of the pioneering work carried out one quarter century ago which not only clearly formulated the concept but also documented therapeutic benefit with hemodynamic and clinical studies. Burch has commented on this omission with respect to his own work, and Cohn and Franciosa have referred briefly to an early study using ganglion blocking agent. However most investigators in this field are not acquainted with the early literature.

Lyons and colleagues' in 1947 noted clinical improvement in patients with congestive heart failure due to various causes following the ganglion blocking drug, tetraethylammonium. This was confirmed by others who also observed decrease in venous as well as arterial blood pressure. The beneficial effects were not limited to patients with hypertension. In 1949 Freis and associates measured hemodynamic changes after veratrum viride in hypertensive patients with and without congestive heart failure. Cardiac output and pulmonary arterial pressure remained unchanged in the patients without heart failure. However in the patients with heart failure cardiac output increased and pulmonary arterial pressure fell in association with the reduction of blood pressure.

Kelley and co-workers in 1953 reported on the effect of hexamethonium in congestive heart failure of various etiologies. They documented a fall in venous pressure, shortening of the circulation time, and in most cases a decrease in heart rate. These objective evidences of improvement were accompanied by symptomatic improvement in the degree of dyspnea and orthopnea. The same group in 1953 reported on the hemodynamic changes after hexamethonium. Cardiac output fell and total peripheral resistance remained unchanged in hypertensive patients without heart failure but in patients with congestive heart failure cardiac output rose and total peripheral resistance fell. Right heart pressures fell in both groups of patients, which they attributed to venodilatation.

Kelley and co-workers postulated that hexamethonium may interrupt the congestive failure cycle at two points: (1) by decreasing total peripheral resistance the work demand on the left ventricle is lessened, and (2) by reducing the filling pressure of the right heart the overloaded right ventricle is able to contract more effectively. Except for the absence of the terms "afterload" and preload, this explanation seems quite modern.

It is of interest that the improvement occurred despite the fact that hexamethonium blocks not only alpha- but also beta adrenergic activity. Apparently the beneficial effect of the peripheral vasodilatation far outweighed the deleterious effect of beta-adrenergic inhibition. However alpha-adrenergic blocking agents also were used for the treatment of congestive heart failure many years ago. Brod and Fejfar[11] in 1951 reported on the use of dibenamine in congestive heart failure and observed a decrease in total peripheral resistance and a transient increase in cardiac output. These results were confirmed one year later by Halmagyi and associates.[12]

Today the availability of a greater choice of drugs with more localized and specific effects has increased the therapeutic effectiveness of this approach and broadened the scope of its applicability including the use of vasodilator therapy in patients with myocardial infarction. It is also apparent that the ideal drug has not yet been found[1] and that the present state of knowledge concerning mechanism of action and therapeutic benefit in cardiac failure is not essentially different from that described 25 years ago.

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Physiological sleep patterns and cardiac arrhythmias

While in the past sleep has been considered to be a rather passive state of the organism, more recently it has been shown to be quite the antithesis—an active physiological and biochemical process Of particular interest has been the notion that physiological changes during sleep may be associated with sudden death due t the arrhythmogenic proper ties of sleep, and particularly rapid eye movement (REM) sleep (that phase of sleep most associated with dreaming). Studies in this area have produced quite inconsistent results. Most of these studies ha been navoidably contaminated by the common pitfalls of lin l studies use of heterogeneous patient population m lt plici of patient medications, and the presence of additional medic l problems It was felt that it would be worthwh le t ex luat group of patients who had noct nal bnormal be t h t or nary artery disease, represented homogeneou diag os tegory were not on multiple medications nd did ha additional medical problems Such patie re l epresented than the diagnostic categ i m t l l p l pse MVP) syndrome Four patients w th noc nal bnor l ei selected for evaluation, t m h nd males g g in age from 27 to 60 years The p ese f l l mal beats was either documented by ex h H h ing or inferred from good history of f eq t u l palpit ions

The diagnosis of MVP m h he basis of (1) non ejection click or lick pl d ( ) echocardiographic evidence of MVP I d l patie ts had consistent history of frequent pal patients ere receiving medication t the tim l l F propranolol hydrochloride, diphenylh dan v l d diazepam for arrhythmias and anxiety H h g quinidine

Table 1 Total number of arrhythmias across nights

Pt.	Type	REM (rate/min.)	NREM (rate/min.)	Wake (rate/min.)
L. F	PVC	1.8784	1.7359	2.1046
	PSVC	2.3538	3.9402	3.4520
	Trigeminy	0.1101	0.3764	1.7061
	Bigeminy	0.1683	0.1728	0.0996
	Salvo	0	0.0011	0
	AT	0	0	0
H. K.	PVC	0.2910	0.3515	0.3363
	PSVC	0.0679	0.0441	0.0131
	Trigeminy	0	0	0
	Bigeminy	0	0	0
	Salvo	0.0087	0.0012	0.0026
	AT	0	0.0012	0
T. C.	PVC	0.0224	0.0132	0.0671
	PSVC	0.0973	0.0793	0.1310
	Trigeminy	0	0	0
	Bigeminy	0	0	0
	Salvo	0	0	0
	AT	0.0337	0.0441	0.0671
T. H.	PVC	0	0.0010	0
	PSVC	0	0.0103	0
	Trigeminy	0	0	0
	Bigeminy	0	0	0
	Salvo	0	0	0
	AT	0	0.0021	0

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which was subsequentl determined t be t non therap tic lev ls according to serum assay) P tients re xcluded if they had coronary art ry disease or if their ondition complicated by other medical problems.

Patients slept in the labor tory for three co sec ti ghts during their normal sleeping hours. Electr nc phal gr m (EEG), lectro-oculogram (EOG) and lectromy gram (EMG) ere recorded ll night, long th an lectrocardio gram (ECG) from single V precordial lead. These recordings were arried out simultaneously on Gr ss Model 7 pol gr ph t paper speed of 15 mm sec Each 30-second period of recording was scored as REM sleep, haracterized b movements and low oltage mixed frequency EE and non-r pid ey mov ment sleep (NREM), th 12 t 14 H spindles or 0.5 to 3 H EEG activ t predominating. Abnormal beats were grouped in the follo ing manne prema ure ventricular contractions (PVC), premature supra entricular contractions (PSVC), nd trial tach ardia (AT). V ntricu lar tachycardia (VT) was not documented in of the recordings.

Data ere subjected to analysis of arianc ith the following results. (1) the rate of occurrenc of bnormal be t did not hange across nights or within any one of the nights when divided into thirds, ( ) abnormal be ts did not oc ur ith any more frequency in REM han in NREM (3) no pe of abnormal beats oc urred with any more frequency than an other

Despite the fact that man contaminating ariables had been liminated with this patient group, these data still contained considerable night to-night ariabilit (Table I) It is interesting to note that not onl did the numbe of abnormal beats per minute ary from over 8 per min t in L. F to 1 per 7 hours in T H., but even within the same patient there was great ariability across nights. T H who displayed several types of abnormal be ts t night during screening, showed total of only nine abnormal beats in three consecu. th study nights. The total number of abnormal be ts for an individual in this admittedly small group did not seem to be altered by REM sleep.

While these observ tions do not xclude the possibility of abnormal beats being altered by sleep or REM sleep in some MVP patients, they do suggest that this is not routinely occurring phenomenon. The considerable ariability from night t night in the inciden of the arious abnormal be ts prese ts many problems for the linicia in terms of classify ing pat ts as high risk for sudden de th, hich is known to be ssociated w th MVP

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Letters to the Editor

AH and HV intervals in children with heart *disease*

T the Editor

There are only a limited number of reports on the AH and HV intervals in infants and children. Discrepan ies in the intervals and their correlation with various factors such as age and heart rate are noted, which are due to the limited umber of patients reported in the literature. Accumulation of more data is necessary in order to allow comparison of values.

We obtained His bundle electrograms in 60 children with heart disease (43 with congenital defects, 8 with chronic rheumatic v lvular lesions). The patients ages ranged between 50 day t 14 years (mean = 7.46 yrs.). The AH interval (mean ± SD) was 93.00 ± 31.79 msec., whereas the HV interval was 54.26 ± 14.47 msec. These values are loaest to those reported by Brodsky and colleagues. Lik Gillette and associates, we did not notice any correlation between these intervals with patient age. Moreover there was no correlatio bet een either AH or HV intervals with the heart rate. Lack of correlatio of HV interval with heart rate was also noted by Cohen and co-workers' however the in erse correlation of AH interval with heart rate' was not significant in our material.

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Complications with heparin therapy

To the Editor

In the report by Dr rs M M lis nd Strate (Fibrin deposition on pacemaker heter in heparinized patient, AM. HEART J 95 405 1978 pa ien treated with heparin 7,500 units every four hours (given by intravenous push) to produce slight prolonged partial thromboplastin time 3.5 hours after each dose is later described by phrases such as "well heparinized" (*sic*), "full therapeutic doses, an adequate heparin therapy

The writers are asking the reader to assume a state o anticoagulation that may not ha e existed. If fibrin or thrombus deposition or ther complication was observed to occu following constant infusion heparin therapy monitored with reproducible partial thromboplastin times of t o to thre times baseline values, one would be more certain tha adequat heparin therapy had, in fact, been chieved, and tha the complication occurred in spite of t.

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Normal initial vectors on the ECG

To the Editor

Prompted by the observ tion of Jacobsen and associates' that electrocardiographic evidence of initial left to right forces occurs less frequently with a normal frontal plane QRS axis than in the presence of superior axis, w repeated their study analyzing 2,000 consecutiv electrocardiograms of hospital patients. One hundred eighty two patients were excluded because of complicating factors such as conduction disturbance or evidence of inferior or lateral infarction, leaving a study group of 1,818. I this survey septal" Q w es were present in Leads I and/or V in only 27 per cent of patients whose frontal plane axis as zero to +90 degrees. Like Jacobsen and associates, w found that the more superior the QRS axis, the more common the identification of septal Q w es.

Table I Per cent septal Q present in Leads I and/or aV

Frontal QRS axis	*Bergen Pines study (1,818)*	*Jacobsen study (343)*
0 to +90	27	42.5
0 to −44	57	64
−44 to −90	61	73

These results are contrary t the usual teaching that normal initial depolarization identified on lectrocardiograms is from left to right. W presume that the absence of normal" initial forces in nearly three quarters of this large inpatient survey reflects our hospital's rather elderly patient population Therefore, t would be inappropriate to extrapolat from this data t ambulatory healthy younger individuals.

Nonetheless, the data underscore the continuing clas

problem of what constitutes normal initial vectors as recorded on the electrocardiogram. Neuro-anatomic and electrophysiologic studies have indicated that the trifascicular concept of the left bundle is an oversimplification. Since the left bundle subdivisions often include a presumably functional middle septal division, depending on their extent, depolarization of these fibers [illegible] should have some identifiable electrocardiographic expression. The difficulty of precisely localizing lesions in the His-Purkinje system according to electrocardiographic patterns is demonstrated further by recent observations that bundle branch and divisional block patterns may be caused by conduction delays originating either more proximal or peripheral to the major divisions.

Therefore, it is necessary that the electrocardiographer be aware of the limitations of the technique in order to avoid the pitfall of overinterpretation. On the other hand, conventional electrocardiography may contain more information than is commonly derived. For example, additional study is required to define the contribution of left middle division fibers to both normal and abnormal initial vectors.

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Orthostatic increase in blood pressure in the elderly

To the Editor:

We were greatly interested by the article by Hull and associates entitled "Borderline hypertension versus normotension: Differential response to orthostatic stress."[1] The authors very properly stress the value of this particularly valuable test which consists of the measurement of blood pressure in an erect position in order to reveal sometimes large increases in blood pressure in cases of apparently moderate hypertension, or in order to reveal hypertension in an individual who is normotensive in supine position at rest. Their study involved young or middle-aged men, but we feel that the prevalence of orthostatic hypertension in the elderly subject has not yet been sufficiently noted.

At the end of a preliminary study involving 75 *elderly subjects*, a similar work was undertaken in 200 *inmates of an old people's home*. Their average age was 80 years and they were unselected. The results were *quite unexpected*. Attention has always been drawn up to the present time to the risks in the elderly of orthostatic hypotension, with the possibility of syncope from cerebral ischemia. Nevertheless an orthostatic fall in blood pressure was found in *only 14 percent of our* cases, almost always moderate and with no detectable clinical consequences. By contrast, *hypertension* persisting after the effort of maintaining an upright position was found in 31 per cent of cases with an increase in mean arterial blood pressure *of 10 mm. Hg or more*. The proportion of blood pressure increase was not essentially different in the 113 subjects considered to be normotensive in lying position, (24 per cent) and in the 77 individuals initially considered to be hypertensive (i.e., 48 per cent).

It is most likely that this orthostatic hypertension is one of the features of labile hypertension so common in the elderly even though it is produced by mechanisms which appear to differ greatly from those involved in the young subject. Such labile hypertension may be revealed by different types of stress, including orthostatic. The sympathetic stimulation which results from changing to an upright position seems to be inadequately counterbalanced by a decrease in the sensitivity of the baroreceptors with a regulating action found in the arterial walls. By rendering the vessels less distensible, atheroma hampers the response of the baroreceptors which are sensitive to variations in transmural pressure. As mentioned by Hull and colleagues, such orthostatic hypertension should not be unrecognized or neglected, in view of the length of time which the patient may spend daily in the upright position. As in the young subject, it may be supposed that this orthostatic increase in blood pressure favors the development of atheroma in the elderly, especially in the cerebral circulation. If this hypothesis were to be confirmed, appropriate hypotensive therapy would be justified, especially in certain elderly subjects in whom this orthostatic increase in blood pressure is particularly marked and confirmed by several successive examinations. At all events, given the ease with which such study may be carried out, we would hope that it might be applied on a wider scale and confirmed in a much larger population of ambulatory elderly subjects apparently in good health.

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Reply

T the Editor

W are greatful to Dr Max Berkman and his colleagues for drawing our attention to work on the orthostatic responses of elderly subjects. Several studies of old people' ha e described orthostatic hypotension as quit frequent, though an underlying causatn abnormality might be discerned in many if not in most subjects in whom it was sought. Health disorders, often multiple, are obviously frequent in old ge, are liable to escape detection, yet are almost certainly over represented in those populations most readily studied—that is, the inactive and instit tionalized. In one study great care was taken to select only healthy normal lderly male subjects; their orthostatic responses were indistinguishable from those of young men. Thus, orthostatic hypertension might reasonably be expected in some otherwise healthy old people.

Although the merits of antihypertensive treatment in the aged remain somewhat uncertain, we applaud Dr Berkman call for further study of the orthostatic responses of pparent ly healthy old people, some of whom may well benefit from judicious risk factor intervention.

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Risks of early commissurotomy

T the Editor

I wish to commen on Dr Frank Spencer article in the May 1978 issue of he AMERICAN HEART JOURNAL. A plea for early open mitral ommissurot m (93 668, 1978). In this article Dr Spencer pers ass l arg s t earl ommissurot omy in patients with minimal mpt m owing t mitral stenosis. His argumen are that the isk is small (mortality rate 1 t 3 per cent), tha he pera ion is mor ffectiv when carried out before bea a in tion and more severe symptoms ppear and that he has ser no idenc of restenosis in follow-up up to ten years. As D Spe point out, there is group of patients in whom com missur om is ry effectiv and certainly mitral alv replacement is not necessary for every patient with symptomatic mitral stenosis. H indicates that we have no controlled clinical trial to ev luate his suggestion and it is unlikely that w will ha e one.

Dr Spencer may be right in his suggestion, but in the absence of a controlled trial it is important to point out some implied assumptions and undesirable aspects of the course he suggests. As Dr Spencer admits, as a rule the course of progressive mitral stenosis is quite slow and it may well be several decades before the patients to whom he refers become sufficiently disabled that surgical treatment becomes manda tory

To follow Dr Spencer recommendation assumes that every surgeon can accomplish the proper patient selection and will achiev the excellent results and the low mortality rate that he describes. This assumption in many instances may not be justified and thus the mortality rat of the procedure may well exceed the 1 t 3 per cent figure that he mentions, and there may be more omplications. Dr Spencer say little about the complications of open mitral commissurotomy except for one ery important one, nd that concerns the small number of patients who developed mitral insufficiency later on. W are not told what happened t those patients. It is very likely that some of them require val replacement, which carries a much higher mortality rate than the one cited in his paper namely from 5 to 15 per cent even under ideal circumstances, not to mention their more uncertain f ture course after al replacement. It would be good t know how many of Dr Spencer patients, originally planned for mitral commissurotomy immediately or eventually recei ed mitral prosthetic alves, either because satisfactory relief of stenosis could not be obtained or because mitral insufficiency was produced.

Dr. Spencer article implies another unproved assumption, namely if one looks ahead some 20 or 30 years from the time the patient is operated upon, that his patients will necessarily be less symptomatic than patients who are treated medically Although he has observed no restenosis within the last ten years, what will be found after 20 and 30 years? As he points out, the damaged mitral val tends t stenosis and repeated attacks of rheumatic fever or continuing activ rheumatic fever are not essential t the process. Indeed, restenosis has been reported in most large series of patients who ha had mitral commissurotomy The incidence of restenosis after ten years has been reported to be from 10 t 50 per cent.

Dr Spencer article takes no account of certain other negative features of the course that he espouses, although they are perhaps less important than those already discussed. These include the expense of the surgical treatment that he suggests—well over $10,000 minimally the loss of time, and the pain and discomfort of the procedure and the development of certain unpleasant, usually non-fatal, complications. Among these is the post-cardiotomy syndrome. I some 10 to 30 per cent of instances the operated patient may be expected to develop one or more ttacks of painful febrile pleuropericarditis. These, in themsel es, may require hospitalization for treatment although they usually do not lead to permanent sequelae. Then there is the incidence of hepatitis (1 to 2 per cent or more) if blood is used in the priming of the pump for the cardiac surgery

Finally there are in Dr Spencer recommendations some philosophic issues that are also to be found in other areas. I

refer specifically t current recommendations by surgical enthusiasts for coronary bypass grafting in patients ith asymptomatic or minimally symptomatic coronary artery disease. These recommendations seem to say something lik this: "If surgical procedure ca be carried out with low mortality rate, namely 1 per cent, 2 per cent, or 3 per cent, there is no need to prov that the results are better than those of medical management. When expert cardiac surgeons operate upon patients with minimal symptoms or no symptoms, the mortality statistics are usually good but they fail t furnish us evidence that such operations are necessary. As surgical and diagnostic techniques improve, the tendency is to operate upon earlier and milder forms of heart disease, but do not really know the natural history of these diseases. Previous diagnostic and surgical perience with more advanced forms of the same disease does not provide that information. One can easily imagine the difficulty in obtaining FDA approval of new drug associated with risk of this magnitude. If there is to be no controlled clinical trial, the thoughtful physician should t least wish t consider some of the uncertainties and potentially unfavorable aspects of Dr Spencer suggestion.

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Reply

T the Editor:

I appreciate the opportunity of responding to Dr. Noble Fowler critique of my therapy article on early open mitral commissurotomy appearing in the May 1978, issue of the AMERICAN HEART JOURNAL. I studied Dr. Fowler comments carefully and repeatedly because his experiences, contributions, and judgment in American Cardiology for decades are both widely know and respected. My comments will be fairly brief because, as I indicated in the article, these are suggestions without control data, because with the slow evolution of the disease in many patients, true randomized control study will probably never be possible. Without data, one can only suggest possibilities but scientifically valid conclusion is not possible.

For emphasis, I would like t repeat the major changes that prompted the writing of the article, for many of the data from surgical operations before 1970 are simpl no applicabl for present considerations. The advances are at least fi

First, the operation of open mitral commissurotomy is extremely safe, with several centers reporting series of 100 or more patients with no mortality. As Dr. Fowler indicates, this does not indicat that the operation should be done simply because it is safe, but does indicate the safety of operation if it is undertaken.

Second, the proper operation is far more radical than hat was considered adequate in past years. This is accomplished by separation of fused chordae and papillary muscles under direct vision, striving to obtain alvular orifice with cross-sectional area as close t normal as possible. In retrospect, the closed procedures of past decades simply enlarged an orifice near 1.0 cm. to one near the 2.0 to 2.5 cm. range, with resulting restenosis in high percentage with subsequent recurrence of the disease within fi years in nearly 50 per cent of patients. Dr. Fowler refers to these data but, to repeat, these data are simply not true with present techniques, for our own group and several other groups ha not observed re-stenosis over period of fi to ten years in patients in whom the gradient between the atrium and entricle was eliminated and large cross-sectional area was obtained.

Third, this radical operation of separation of chordae and papillary muscles has become possible only by technical advances which permit the detection and correction of mitral insufficiency t the time of operation, as described in the article and in previous publications. Without this ability to detect and correct mitral insufficiency surgeon would naturally be fearful of opening the alve "too much." Dr. Fowler asked about the frequency with which patients develop mitral insufficiency afterward. I hesitate to speak in percentages because this has been so rare, but my impression is that this is less than 5 per cent in our patients in the last several years.

Fourth, routine closure of the atrial appendage has virtually eliminated the problem of thromboembolism in patients following operation if the stenosis is corrected, even though atrial fibrillation remains. Before this was routinely done, a rare patient still developed emboli, even though mitral stenosis was no longer present.

Finally, it seems almost certain from our current understanding of the pathology of mitral stenosis, that the longer operation is postponed, the more the valve leaflets will be injured from progressive fibrosis and calcification from the *effects of turbulent flow of blood. Accordingly, the possibilities* for surgical correction without producing insufficiency or performing prosthetic replacement will be progressively decreased. Also, the likelihood of permanent atrial fibrillation, of lesser importance, becomes almost certainty.

Hence, the suggestions were made in the editorial that operation be considered much earlier than in the past. The economic question posed by Dr. Fowler I do not understand. Certainly an operation is expens e, but if 40-year-old male is restored to normal health and protected from potentially devastating cerebral embolus over the next three decades of life, the economic savings are clear. It is similarly clear that ailable medical therapy may minimize the effects of mitral stenosis by slowing the heart rate and minimizing the retention of sodium, but there is no way that the stenotic valve can be made larger. On the contrary, the best that can be hoped for with medical therapy is that the stenotic process will not progress at rapid rate. What is not know is how many patients can be managed throughout their lifetime without operation and yet lead producti lives. Hence, returning to

the original suggestion, if cardiac catheterization demonstrates that the cross-sectional area of the valve has been decreased to the range of 1.3 to 1.5 cm, why should operation be postponed?

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Second-hand pacemakers

To the Editor:

I wish to draw the attention of your readers to the possibility that a "second-hand pacemaker" market is fast becoming a reality.

From figures published by Parsonnet, which broadly agree with the number of pacemaker implants in Western Australia, we can assume that 270 implanted pacemakers per million population per year represents a realistic number of implants for the population of the Western developed world. Assuming a total population of 500 million in that area, the total number of implants per year is 135,000. As the mortality rate from pacemaker-unrelated causes in patients in this hospital is about 6 per cent per year in the first two years after implant, we estimate that approximately 10,000 pacemakers per year may become available for reuse in the western world. These, if resterilized and resold with a profit margin of $100, could form the basis for a million dollar industry, especially when the price of $1,200 or higher for new six year lifetime pacemakers is taken into consideration.

Unscrupulous practices can be envisaged. We face, in fact, a completely new situation namely because, as Dr. Parsonnet has pointed out, the pacemaker represents the only truly successful active "organ" yet manufactured and now these are available with a reliable six year or longer life-span.

May I be allowed to suggest that an international organization, such as the W.H.O. or the various national Heart Foundations, should be asked to become the international organizers and beneficiaries of such a venture, working on a low profit basis and applying stringent hygenic, medical, and ethical controls.

I hope that others will feel encouraged to present their views on this issue.

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Book reviews

Cardiac Arrhythmias: Electrophysiologic Basis for Clinical Interpretation. By Yoshio Watanabe, M.D. and Leonard S. Dreifus, M.D., New York, 1977 Grune & Stratton, Inc., 373 pp. Price $29.50.

Many books have been appearing regularly on cardiac arrhythmias since the original classic, "Clinical Disorders of the Heart Beat" by Sir Thomas Lewis. Interest in cardiac arrhythmias has increased in recent years due in large part to more extensive monitoring of the heart and to the use of digoxin simultaneously with salt restriction diets and the use of kaliuretic diuretics. Many of the complex arrhythmias are extremely difficult to interpret and many even have more than one reasonable interpretation. This book reviews the patho-electrophysiology of the common cardiac arrhythmias. Unusual ones are also discussed. The relationship of disturbances in heart rhythm to structural diseases is also emphasized to relate the arrhythmia to the clinical problems that confront the physician. Management is also discussed. This is a book intended for the practicing physician. It is a good book, but it must be read critically and thoughtfully for the reader to appreciate it fully. This is a good addition to the other books now available on the subject.

Pathology of Ischaemic Heart Disease. By Sir Theo Crawford, London, 1977 Butterworth & Co., Ltd., 170 pages. Price $21.86.

This is one of the volumes in the series on Postgraduate Pathology. Like the other volumes, this volume is intended to be used for training in pathology. However, cardiologists, trainees in cardiology, and physicians who treat patients with heart disease will find this to be an excellent, concise, and lucid presentation of the pathology of the heart with ischemic disease in a little over 150 pages. The clinical discussion and the etiology of coronary artery disease really adds very little to the book. A great deal is known about the pathology of ischemic heart disease but little is known about etiology and pathogenesis of coronary arteriosclerosis. Sir Theo, an authority in pathology, could have used those pages to describe the ultrastructural changes noted in ischemic heart disease. Regardless, this is a very good book for students and others studying diseases of the heart. The illustrations and brief bibliographies are well selected.

Advances in Cardiopulmonary Resuscitation. Edited by Peter Safar, New York, 1977 Springer-Verlag, 302 pages. Price $22.50.

This book represents the proceedings of a symposium held during October 1975. The subjects discussed include the prearrest period, airway obstruction and respiratory arrest, circulatory arrest, drugs, electrocardiography, pacing and defibrillation, the immediate postresuscitative period, special considerations, and historic vignettes. Many of the contributors were responsible for the establishment of the technic and instrumentation of managing cardiac arrest. Most cardiologists and other physicians will find this to be a very good book to own, even though they may consider their knowledge of cardiopulmonary resuscitation to be adequate. Among the special considerations are the problems of near-drowning, intrauterine fetal resuscitation, and legal considerations. The subject is well presented, and the presentations are well written. It is a book that would be useful in all coronary care units, emergency rooms, and physicians' libraries.

Progress in Cardiology. By Paul N. Yu and John F. Goodwin, Philadelphia, 1977 Lea & Febiger Publishers, 211 pages. Price $15.00.

This volume is concerned with selected aspects of coronary arterial surgery and coronary surgical care versus medical care of ischemic heart disease. The treatment of ischemic heart disease is a timely subject. The many contributors present the medical and surgical approaches to therapy very well. These discussions are based primarily upon data in the literature. However, the reports in the literature are accepted implicitly and not critically. The presentation by Bristow summarizes very well his opinion of the approach to the management of ischemic heart disease accepted by most cardiologists. As usual, the various authors who discuss the pros and cons of surgery tend to advise waiting for more time to determine the indications for surgery, method of selecting patients for surgery, and the evaluation of the medical and surgical management. The discussions and criticisms of the role and indications for cardiac catheterization in the evaluation of left ventricular function, which appears to be a general requirement prior to surgery, is not discussed. The accuracy of reported deaths and serious accidents in the catheterization laboratories is essentially ignored. Some patients do die in the catheterization laboratory in the USA and their deaths are not described in the medical literature. Thousands of patients have had cardiac and coronary artery catheterizations, sufficient to learn the final outcome. These patients need careful investigation even in the large centers that report good results, as well as in the small hospitals, clinics, and doctors' offices where the procedures are used or recommended to patients. Coronary artery surgery is an important, extremely hazardous, and expensive problem in the delivery of health care throughout the world. Furthermore, do we need to train more and better cardiologists or more and better cardiac surgeons? The important VA cooperative study of coronary arterial surgery is included in this book. Some of the other contributors tend to ignore their study which is still under investigation and in some of best VA Hospitals in America. This book is a good publication. This reviewer advises all physicians to read it critically and establish their own opinions concerning the treatment of this important problem.

SI Units in Medicine: An Introduction to the International System of Units with Conversion Tables and Normal Ranges. By Herbert Lippert and H. Peter Lehmann, Baltimore, Munich, 1978, Urban and Schwarzenberg, 211 pages. Price $14.50.

Clinical EKG Guide. By O. H. L. Bing, M.D Annapolis, Md., 1977 Chastain-Tilghman Books, 42 pages.

Handbook of Clinical Pharmacology By F Bochner G. Carruthers, J. Kampmann, and J Steiner Boston, 1978, Little, Brown & Company 313 pages. Price $9.95.

The Infection-prone Hospital Patient. Edited by John F Burke and Gavin Y Hildick Smith, Boston, 1978, Little, Brown & Company 252 pages.

The Practice of Coronary Artery Bypass Surgery By Donald W Miller, Jr New York, 1977 Plenum Publishing Corp., 227 pages. Price $19.50.

Practical Echocardiography A Basic Manual. By C. David Joffe, M.D., Bowie, Maryland, 1978, The Charles Press, Publishers, 193 pages. Price $18.95.

Problem Solving in Immunohematology By Arthur Simmons, Chicago and London, 1977 Year Book Medical Publishers, Inc., 204 pages.

Coronary Artery Surgery By John L. Ochsner and Noel L. Mills, Philadelphia, 1978, Lea & Febiger, Publishers, 275 pages. Price $25.00.

Announcements

International Society for Heart Research meeting

The second biennial meeting of the International Society for Heart Research, American Section, will be held in Ottawa, Ontario, Canada, from May 17 through 19, 1979. Further information regarding registration and participation in this meeting can be obtained from. Department of Physiology University of Ottawa, Ottawa, Ontario, KIN 9A9, Canada.

Exercise therapy for the cardiac patient

A course entitled "Exercise therapy for the cardiac patient, will be presented in Houston, Texas, on February 9 and 10, 1979, under the sponsorship of Baylor College of Medicine, Departments of Physical Medicine and Medicine. Guest speaker will be Nanette K. Wenger M.D of Emory University School of Medicine. The course will be conducted at the Houston Marriott Hotel (Astrodome) 2100 S. Braeswood Blvd. at Greenbriar Houston, Texas 77030. For further information, please contact: Office of Continuing Education, Baylor College of Medicine, Texas Medical Center Houston, Texas 77030. Phone (713) 790-4941.

Seventh Annual Surgical Intensive Care symposium

The seventh annual Surgical Intensive Care symposium will be held at the Eden Roc Hotel, Miami Beach, Fla., on May 4 through 7 1979. The symposium is sponsored by the University of Miami School of Medicine, Departments of Anesthesiology and Surgery Twenty hours of continuing medical education credit will be granted. For further information regarding the symposium, contact: Division of Continuing Medical Education, D23-3, University of Miami School of Medicine, P.O. Box 016960, Miami, Fla. 33101. Telephone (305) 547-6716.

American Heart Journal

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Editorial

Propranolol in clinical medicine

Raymond P Ahlquist, Ph.D F.C.P
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The adrenergic receptor mechanism has been recently reviewed in this JOURNAL.[1] The primary action of propranolol is to block competitively the *beta* adrenergic receptor Although there are more than 15 *beta*-blockers available in other parts of the world only propranolol has been approved for use in the United States. Therefore, while only propranolol will be considered, everything said applies equally to any other *beta* blocker

The clinically relevant *beta* receptors are those of the heart, blood vessels, bronchial smooth muscle, and the juxta glomerular apparatus of the kidney The most obvious effect of the administration of propranolol to a patient is sympathetic denervation of the heart. Depending on the dose (blood level), this can be a partial denervation or an almost total denervation. Bradycardia always occurs, A V conduction is slowed the myocardium is depressed if there is sympathetic action present when the propranolol is given. Cardiac output is diminished, and since there is no immediate change in arterial pressure, the calculated peripheral resistance is increased.

Adrenergic bronchodilation is prevented by propranolol. This has no effect on airway resistance if obstructive lung disease is not present. Plasma renin activity is diminished by propranolol, but in the absence of hypertension this has no significant effect on arterial pressure or sodium retention. All of these actions of propranolol are reversible by the administration of adequate doses of isoproterenol.

Propranolol is used clinically to produce a partial cardiac sympathectomy In angina pectoris this effect increases exercise tolerance by diminishing the cardiac response to exercise. In idiopathic hypertrophic subaortic stenosis, propranolol often has a beneficial effect by this same mechanism. Propranolol is effective in most tachyarrhythmias. Sinus tachycardia, whether from thyrotoxicosis or congenital, is diminished by propranolol. The tachyarrhythmias of ventricular origin are often slowed by propranolol. This effect is based on the fact that most fast ventricular arrhythmias have a sympathetic component.

Propranolol is a local anesthetic and has a quinidine-like action on the heart. This action is clinically irrelevant since the blood level achieved with the usual oral dosage is too low It should be kept in mind that this myocardial depressant action may appear if daily oral doses above 1 Gm. per day are given to patients with severely *diseased hearts.*

The important use today for propranolol is in the treatment of hypertension. If we list the desirable properties of a good antihypertensive agent, it can be shown that propranolol can be considered as the drug of first, and only choice for treating essential hypertension.

From the Medical College of Georgia, Department of Pharmacology Augusta.

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Reprint requests Raymond P Ahlquist, Ph.D Medical College of Georgia, Dept. of Pharmacology Augusta, Ga. 30901.

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What are the characteristics of a good antihypertensive agent? How does propranolol fit with these ideals?

1. It should be the only drug needed.
2. Relatively infrequent doses should be required.

Propranolol fulfills both of these requirements. It is the only drug needed in about 70 per cent of patients and only two doses per day need be given.

3. The drug should have long term effectiveness and safety

Some patients have been taking propranolol for more than 12 years. The drug continues to be effective and no unexpected toxicity has appeared.

4. The drug should be effective in most patients.

There are estimates that propranolol is effective in 70 to 90 per cent of patients with essential hypertension. This figure varies with patient populations tested, with geographic location, and with the *preferences* and prejudices of different investigators. It should be noted that most clinical trials are done on highly selected clinic patients. Often these patients are not really true representatives of the general population.

5. The drug should not produce postural hypotension.

Propranolol does not produce postural hypotension. Unlike most other antihypertensive drugs, propranolol is effective whether the patient upright or recumbant.

6. Adverse actions should be predictable, preventable, and reversible.

Most of the adverse effects of propranolol are due to *beta* adrenergic blockade. These actions are, *therefore*, predictable. With proper patient selection, serious adverse actions are preventable.

7 The drug should not adversely effect life-style.

Antihypertensive therapy should not make a patient feel bad. Propranolol seldom produces impotence. This is very important in the asymptomatic, young male hypertensive. It is of interest to note that "blood pressure medicine" has a reputation of impairing sexual function. Therefore, if propranolol has this effect in certain patients it is difficult to tell whether it is physiologic or psychogenic. Placebos have produced impotence.

8. The *drug* should prevent or diminish the cardiovascular responses to stress which may be exaggerated in hypertensive patients.

Propranolol has been shown to have this effect in *experimental stress*.

9 The antihypertensive drug should have a beneficial effect on cardiovascular disorders often associated with hypertension.

Propranolol is *effective* in angina, tachyarrhythmias, and anxiety There is good evidence that propranolol tends to prevent sudden death following myocardial infarction. However in diabetes, propranolol can mask the *symptoms of* hypoglycemia thereby making the control of blood sugar more difficult.

How to use propranolol. The opinions and conclusions given here are based on observations and discussions in Germany Great Britain, Japan, Southeast Asia, and Canada.

Patient selection is important. Absolute contraindications are. untreated congestive failure, heart block, asthma, emphysema, and peripheral vascular disease. It is probably not necessary to start with an intensive, expensive work up to exclude secondary hypertension, 95 per cent of all hypertension is essential. This is especially true in patients discovered during screening programs to have mild or moderate hypertension.

Start therapy with a small dose 10 mg. four times a day is suitable. Only the first dose is hazardous since this produces an unknown degree of *beta* blockade in the face of an unknown amount of sympathetic activity If this initial dose is safe but non-effective, the daily dose can be doubled about every two weeks.

When an effective dose is found the daily dose may be given in two parts, morning and evening. This is not true when using propranolol for angina. In this case the drug must be given at more frequent intervals. Unlike some other antihypertensive drugs, rebound hypertension will not occur if a daily dose is omitted. What is the maximal dose? In the United Kingdom 960 mg. per day is considered by many as the top dose. In the United States 320 to 480 mg. per day is considered maximal. In a practical sense there is no upper limit to the dose since the main action of propranolol is *beta*-blockade. However as noted above, the higher doses may start to produce myocardial depression.

Propranolol is rapidly cleared by the liver This "first pass" clearance varies from patient to

patient. Therefore, it is difficult to directly relate oral dosage to blood level. There is only a small variation with intravenous doses, 5 mg. produces about the same effect in all patients. This phenomenon is not unique to propranolol. Many other drugs share this inter individual oral dosage variation.

Heart rate changes are a good index to beta blockade. Propranolol always produces bradycardia. The slow heart rate is of little clinical significance unless it produces obvious ill effects such as angina or shock. It is more useful to determine the degree of decrease in the tachycardia due to exercise. Obviously the blood pressure must be monitored. It is probably best if the patient can do this at home.

What are the adverse reactions that might occur? Cold extremities, indigestion, fatigue, and bronchospasm are due to beta-blockade. These are dose-related and are not considered as serious in otherwise asymptomatic patients. Propranolol may also produce some central nervous effects including vivid dreams, hallucinations, paresthesias, and depression. And as with most other drugs, skin rashes and alopecia have been reported. In one large series of hypertensive patients followed for 10 years, 10 per cent were unable to continue taking propranolol and in 14 per cent there were dose-limiting adverse effects.

Propranolol does have certain disadvantages. Some patients do not respond to the antihypertensive action. A diuretic should then be added or substituted. If this is not effective, other antihypertensive drugs should be given. Propranolol plus a vasodilator is a logical combination the *beta* block will prevent the excessive tachycardia produced by a vasodilator such as hydralazine.

Many physicians are concerned because the exact mechanism of antihypertensive action of propranolol is not known. It should be pointed out that this is also not known for most of the other antihypertensive agents. A comparative *examination of all of the beta-blockers now in use* world wide (there are 17 in use in West Germany) gives some insight into this problem.

Some are lipid soluble. This means that they are rapidly cleared by the liver and will penetrate the central nervous system. Some are not lipid soluble and are not cleared by the liver and do not enter the central nervous system. Some are local anesthetics, some are not. Some are partial agonists (intrinsic sympathomimetic action, ISA) some are not, including propranolol. *Beta* blockers with ISA may produce less bradycardia. Some *beta* blockers are cardioselective, most are not. All are effective as antihypertensive agents, and all of them decrease plasma renin activity. Therefore, it can be concluded that the antihypertensive effect is related to *beta* receptor blockade including the renal *beta* receptor controlled renin release. In the case of those which enter the central nervous system, such as propranolol, a central antihypertensive action may also be present.

The cardioselective *beta* blockers have a theoretical advantage in certain patients. One of these, metoprolol, may soon appear in this country. In patients with obstructive respiratory disease, metoprolol may be effective as an antihypertensive or antianginal drug without producing excessive bronchospasm. The cardioselectivity however is not absolute. It is only relative. Higher doses of metoprolol may still produce acute asthma.

The cost of antihypertensive therapy is an important consideration. It is interesting to note that the cost of antihypertensive drugs is *inversely related to their potential toxicity*. Reserpine, the least expensive, has more serious adverse effects than propranolol, the most expensive. Although at the present time propranolol is most expensive, up to $1 per day it may be the only drug needed. The conventional (in the United States) treatment of a diuretic plus methyldopa plus a potassium supplement can be equally costly.

What of the other *beta*-blockers? It can be argued that since propranolol is a universal *beta* blocker it is the only one needed. However a cardioselective *beta*-blocker should be available. A drug that does not penetrate the central nervous system should also be available. Atenolol is such a drug. Timolol, a *beta* blocker that effectively lowers intraocular pressure when applied to the conjunctiva, should be available. A case can also be made for a drug such as alprenolol that has intrinsic sympathomimetic action. Finally if propranolol had some competition, its cost should come down.

One of the difficulties of obtaining FDA approval for these other *beta*-blockers is the problem of doing randomized, double-blind, placebo-controlled clinical trials in angina or

hypertension in this country This would appear to be unethical since the *beta*-blockers are already known to be effective in these disorders based on extensive clinical experience and trials in other countries. There is no question but that there is a serious drug lag with the *beta* blockers. It was 11 years for the antihypertensive use of propranolol.

As a final testimonial it can be stated, fortunately that propranolol, 60 mg. per day (30¢) has lowered the author's diastolic pressure from about 98 to about 82 without any adverse effect of any kind.

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Clinical communications

Qualitative radionuclide angiocardiography in the diagnosis of corrected transposition

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Cardiac catheterization and angiocardiographic procedures[1] are the most frequently used methods to achieve the correct anatomical functional diagnosis of congenital heart disease. However these procedures carry a small, but definite risk of morbidity or even mortality and involve a relatively high radiation dose to the patient.

Following the advent of short lived radionuclides and the development of the scintillation gamma-camera, radionuclide angiocardiography has made great advances. Currently it is possible to obtain data about the morphology of the cardiac chambers, to measure the ventricular efficiency and to detect and quantitate intracardiac shunts by means of this procedure.

This study was designed to analyze the value of qualitative radionuclide angiocardiography in the diagnosis of corrected transposition, a congenital heart anomaly in which the morphological right atrium relates to the morphological left ventricle and the morphological left atrium with the morphological right ventricle, the pulmonary artery emerges from the morphological left ventricle and the aorta from the morphological right ventricle. These relationships are valid for situs solitus as well as for situs inversus.

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Material and methods

Seven patients with corrected transposition were studied by radionuclide angiocardiography utilizing a mobile scintillation gamma-camera (Ohio-Nuclear series 120), with diverging collimator coupled to a magnetic tape recorder. The results were compared with those obtained by biplane contrast angiocardiography.

The patient was positioned supine in front of the diverging collimator of the detecting head of the gamma-camera, taking care to include the heart and the great arteries inside the detecting field. First, the anterior projection of the angiocardiography was obtained with the surface of the collimator in contact with the anterior wall of the chest. Twenty four hours later the left lateral views were obtained following a second injection of the radiopharmaceutical.

With the patient in front of the detector, the basilic vein was punctured with a No. 22 hypodermic needle, a dosage of 6 to 20 mCi of ^{99m}Tc, as sodium pertechnetate, was rapidly injected. Magnetic tape recording was initiated simultaneously. When radioactivity was observed at the lumen of the abdominal aorta, the recording was stopped. Utilizing a multi-imaging device (Ulti-Mat, Ohio-Nuclear), a sequential series of nine images with an exposure of 1 to 2 seconds each was obtained on an x ray plate from the data stored on magnetic tape.

Visceral situs and location of the apex were analyzed from the images. The characteristics of the great arteries, atrioventricular relationships,

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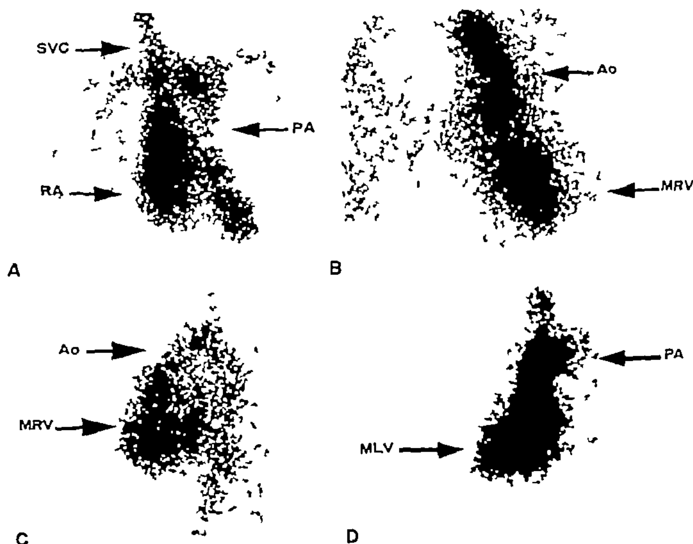


Fig. 1 A through D. Situs solitus with apex to the left. *A*, anterior view. The tracer is at the superior vena ca (*SVC*), right atrium (*RA*), and pulmonary artery (*PA*) which is in a medial position with its branches at the same level. *B*, anterior view. Tracer is at the ventricle placed on the left side (morphological right ventricle-MRV) and aorta (*Ao*). *C*, left lateral view. The tracer is at the morphological right ventricle (*MRV*) and aorta (*Ao*) which is in an anterior position. *D*, left lateral view. The tracer is at the morphological left ventricle (*MLV*) and pulmonary artery (*PA*) which is in posterior position.

and spatial position of the ventricles were determined either from the spatial position of the great arteries or from the morphology of the cardiac chambers.

Results

Visceral situs and apex position were determined in all patients. Four of the five patients with situs solitus had the apex to the left, while one had a right-sided apex (dextroversion). The remaining two patients had situs inversus, one with the apex to the right (mirror image dextrocardia) and the other with the apex to the left (levoversion).

In patients with situs solitus and apex to the left, the pulmonary artery was shown to be in a medial position—to the right of the ascending aorta—with its root attached to the morphological left ventricle, positioned on the right side (Fig. 1*A*). The origin of the aorta was visualized arising from the ventricle placed on the left side (Fig. 1*B*). The aorta was anterior (Fig. 1*C*) while the pulmonary artery was posterior (Fig. 1*D*). The ventricle positioned on the right had a triangular shape (*Fig. 2*).

In the only case with apex to the right, the pulmonary artery was to the right of the aorta with a right to-left direction (Figs. 3*A* and *B*). The ventricle placed to the right was ovoid in shape.

In situs inversus, the pulmonary artery was located to the left of the ascending aorta and emerged from the morphological left ventricle on the left side The ascending aorta, on the right, emerged from the morphological right ventricle forming the upper right edge of the cardiac silhouette. In the patient with levoversion, the morphological left ventricle was ovoid, while the morphological right ventricle was spherical (Figs. 4A B and C). In the patient with mirror image dextrocardia, the morphological left ventricle was triangularly shaped and placed on the left.

Discussion

Corrected transposition, a congenital heart anomaly has been studied by several methods[4-] with the best diagnostic results produced by cardiac catheterization, biplane contrast angiocardiography[14-20] and echocardiography[21]

Radionuclide angiocardiography on the other hand, is of proven usefulness in evaluating patients with known or suspected congenital heart disease and is relatively simple to perform, involving only an intravenous injection of a radionuclide, followed by serial imaging of its transit through the heart and great arteries with a scintillation gamma-camera. This procedure is fast and well tolerated even by severely ill children. The injected volume is small and there are no known or detectable hemodynamic or pharmacologic effects from the administration of the highly specific radionuclide. The radiation dose administered to the patient is considerably smaller than that in the usual radiological procedures.

The resulting sequential series of images produces morphological information about the characteristics of the great arteries, the shape of the ventricles, and the atrioventricular relationships. However this procedure does not supply any data regarding the structural characteristics of the ventricular walls, a fact that partially limits its value.

Due to the specific morphological characteristics of corrected transposition, easily recognized from the sequence of images produced by radionuclide angiocardiography it is possible to diagnose this congenital malformation in the same manner as in biplane contrast angiocardiography[14- 23]

Visceral situs and apex position are relatively easy to determine. In situs solitus with apex to



Fig. 2. Situs solitus with apex to the left. Anterior view showing the tracer as it circulates through the superior vena cava (SVC), right atrium (RA) and morphological left ventricle (MLV) placed on the right with triangular shape.

the left and in mirror image dextrocardia, a triangularly shaped ventricle typical of the morphological left ventricle, can be seen.[14-19] The pulmonary artery shows a posterior medial, and vertical position. Its branches are located at the same level. During the radioangiocardiographic levophase, the anterior aorta is visualized either on the left or on the right, according to the visceral situs.

In both dextroversion and levoversion we were able to identify the ovoid shape of the morphological left ventricle and the anomalous direction of the pulmonary artery[14 16 23]

In the presence of transposition of the great arteries, radionuclide angiocardiography provides indirect data with respect to the spatial position of the ventricles.

These rules were first described by Van Praagh and associates[26 27] and later by De la Cruz and Nadal-Ginard in 1972 for contrast angiocardiography The left and anterior position of the aorta in situs solitus suggests that the morphological right ventricle lies on the left and that it is from this chamber that the aorta emerges. In situs inversus, the right and anterior position of the ascending aorta implies that the morphological right ventricle is located on the right. These two circumstances may lead to the diagnosis of corrected transposition.

However there are exceptions to the rule, as in the unusual forms of transposition,[28] also known

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Abnormal septal motion in patients with postoperative right bundle branch block pattern

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Since the development and clinical application of echocardiography the motion of the interventricular septum has been extensively examined. Ultrasound investigations of the interventricular septum defined the normal pattern of septal motion as well as abnormal septal movement associated with hemodynamic abnormalities. Popp and associates described two types of abnormal and paradoxical septal motion associated with right ventricular volume overload. Subsequently abnormal septal motion was described in patients with ostium primum and secundum atrial septal defects, total and partial anomalous pulmonary venous return,[illegible] tricuspid insufficiency[illegible] and pulmonary insufficiency. The description of a distinctive pattern of septal motion in left bundle branch block[illegible] and Wolff Parkinson White syndrome, type B with right ventricular pre-excitation[illegible] suggested that abnormal ventricular excitation may also produce characteristic echocardiographic features.

The purpose of this study was to examine patients with postoperative right bundle branch block pattern in order to determine the effects of a specific abnormal excitation pattern on the ventricular excitation–contraction relationship as documented by echocardiography

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Materials and methods

Technique. Standard 1? lead electrocardiograms and a complete echocardiogram were performed on all study patients on the same day Echocardiograms were performed on a Hoffrel 101 ultrasonoscope. A hard copy tracing of the echocardiogram and a simultaneous electrocardiogram were recorded on a Honeywell 1856 Visicorder at a paper speed of 50 mm./sec. with one second time lines. An electrocardiographic lead demonstrating a clear q wave was selected for the purpose of measuring intervals from the onset of electrical systole.

The patients were studied in the supine position. An echocardiographic transducer was placed in the third or fourth left intercostal space and positioned to clearly record the anterior and posterior septal surface, the mitral valve apparatus, and the left ventricular posterior wall. In each patient an echocardiographic sweep was made from the level of the mitral valve to the left ventricular apex and then back to the aortic root. All measurements of septal motion were taken from a point at or below the mitral valve chordae to avoid observations from above the hinge point.[illegible]

Fig. 1 is a schematic diagram illustrating the measurements made on each tracing. Time intervals were measured from the echocardiographic tracing on a multiple record comparator with a special vernier measuring device with an accuracy of ±2 msec. Each measurement represents the average of three cardiac complexes, corrected for paper speed. Three parameters were measured on each septal notch (Fig. 1) NH = the maximal notch height in millimeters, was measured from the baseline septal depth to the point of maximal

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Materials and methods

Technique. Standard 12 lead electrocardiograms and a complete echocardiogram were performed on all study patients on the same day. Echocardiograms were performed on a Hoffrel 101 ultrasonoscope. A hard copy tracing of the echocardiogram and a simultaneous electrocardiogram were recorded on a Honeywell 1856 Visicorder at a paper speed of 50 mm./sec. with one second time lines. An electrocardiographic lead demonstrating a clear q wave was selected for the purpose of measuring intervals from the onset of electrical systole.

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Fig. 1 is a schematic diagram illustrating the measurements made on each tracing. Time intervals were measured from the echocardiographic tracing on a multiple record comparator with a special vernier measuring device with an accuracy of ±2 msec. Each measurement represents the average of three cardiac complexes, corrected for paper speed. Three parameters were measured on each septal notch (Fig. 1): NH = the maximal notch height in millimeters, was measured from the baseline septal depth to the point of maximal

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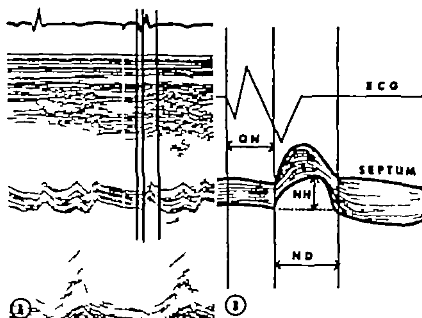


Fig. 1 A and B. A, An echocardiographic tracing showing an early systolic anterior septal notch. B, Schematic drawing of an early systolic anterior septal notch showing the types of measurements obtained in this study NH = maximal notch height, QN = interval from the initial QRS deflection to beginning of the notch, ND = notch duration.

excursion QN was defined as the interval in milliseconds from the initial QRS deflection on the electrocardiogram to the first anterior motion of the left ventricular septal surface ND = the notch duration in milliseconds, was also measured on the left ventricular septal surface, from point of the initial septal deflection to the point of its return to the original depth.

Patients. Three groups of patients were studied. Group I, 20 patients with a normal QRS pattern and duration in Lead V with or without congenital or acquired heart disease Group II, 10 preoperative patients with ventricular septal defect, tetralogy of Fallot or pulmonary stenosis, without evidence of right ventricular conduction delay in Lead V and Group III, 25 study patients with postoperative right bundle branch block pattern Preoperative echocardiograms were not available for patients in Group III.

Pertinent data of Groups I and II is presented in Table I. The 20 patients in Group I ranged in age from 1 month to 16 years with a median age of 8 years. Three had no heart disease and the remaining 17 had a variety of diseases including mitral and aortic valvular disease coarctation of the aorta, patent ductus arteriosus, as well as pericarditis, cardiomyopathy and juvenile rheumatoid arthritis. The 10 patients in Group II ranged in age from 6 months to [illegible] years with a median age of 6 years. There were five children with tetralogy of Fallot, three with ventricular septal defect, and two with pulmonary stenosis. These children had no previous intracardiac surgery Seven patients in Group II showed right ventricular hypertrophy and three patients with ventricular septal defect showed combined ventricular hypertrophy The QRS duration ranged from 0.05 to 0.08 sec. with no evidence of right ventricular conduction delay

Group III consisted of 25 postoperative open heart surgery patients with complete right bundle branch block pattern acquired at the time of surgery A right bundle branch block pattern was defined as an electrocardiogram in which the QRS duration exceeded 0 10 sec. with an rsR configuration in the right precordial leads and a broad slurred S wave in Leads I, aV_L, and the left precordial leads.[11] The clinical, electrocardiographic, and echocardiographic data of the patients in Group III are summarized in Table II The patients ranged in age from 1.5 to 17 years with a median age of 8 years. The interval between surgery and echocardiographic examination ranged from 3 to 93 months, with a mean interval of 38 months. Eighteen patients had tetralogy of Fallot, three had valvular and infundibular pulmonary stenosis, two had ventricular septal defect, and one each had pulmonary atre-

Table I Age range, diagnosis and pertinent electrocardiographic and echocardiographic data on Control Groups I and II

Patient	*Age (yrs)*	*Diagnosis*	*QRS (sec.)*	*ESASN*
Group I				
1	4/12	AS	0.05	NO
2	16	MCS	0.06	NO
3	7	MS	0.07	NO
4	6	P	0.06	NO
5	11	JRA	0.06	NO
6	5	C	0 06	NO
7	3	JRA	0.06	NO
8	1/12	PDA	0 05	NO
9	16	AA	0.06	NO
10	3/12	VSD	0 05	NO
11	15	CA	0.07	NO
12	18	NHD	0.06	NO
13	12	MCS	0.06	NO
14	14	MI	0 07	NO
15	3	C	0 05	NO
16	6	NHD	0.05	NO
17	6	NHD	0 07	NO
18	11	AI	0.04	NO
19	8	CA	0 07	NO
20	13	MCS	0.06	NO
Group II				
1	6	TOF	0.06	NO
2	6/12	VSD	0.06	NO
3	1	TOF	0.06	NO
4	7	TOF	0 06	NO
5	6	VSD	0 06	NO
6	6/12	TOF	0 06	NO
7	7/12	TOF	0.06	NO
8	7	PS	0 06	NO
9	8	VSD	0 06	NO
10	2	PS	0.06	NO

Abbreviations: AA = aortic aneurysm; AI = aortic insufficiency; AS = aortic stenosis; C = cardiomyopathy; CA = coarctation of aorta; ESASN = early systolic anterior septal notch; JRA = juvenile rheumatoid arthritis; MCS = mitral click syndrome; MI = mitral insufficiency; MS = mitral stenosis; NHD = no heart disease; P = pericarditis; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

ma with ventricular septal defect and primum atrial septal defect. All children in Group III had a QRS duration greater than or equal to 0.12 sec. and complete right bundle branch block pattern.

The 25 patients of Group III were further subdivided into two groups. Group A consisted of 19 children with QRS duration ranging from 0 12 to 0.16 sec., frontal QRS axis from −10 to +225 degrees, and a clockwise or figure-of-eight frontal plane QRS loop. Group B included six patients with QRS duration ranging from 0.12 to 0.14 sec., frontal QRS axis of −30 to −120 degrees, and a counterclockwise frontal plane QRS loop, the so-called right bundle branch block and left anterior hemiblock pattern.

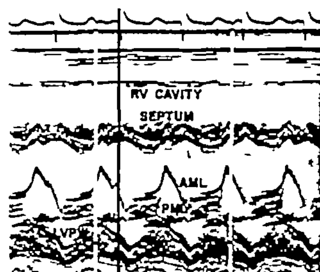


Fig. 2. Echocardiogram demonstrating normal motion of the interventricular septum, left ventricular posterior wall (*LVPW*), anterior mitral leaflet (*AML*), and posterior mitral leaflet (*PML*). *The perpendicular bar* on the septum marks the initiation of the QRS complex in the cardiac cycle. Note the absence of any early systolic anterior motion or notch in the period immediately following the bar marker.

Results

All control patients in Groups I and II had normal QRS patterns without evidence of a right ventricular conduction delay and all had normal septal motion as previously described (Fig. 2).[1, 20]

In contrast, each patient in Group III with postoperative right bundle branch block pattern demonstrated a characteristic abnormality of septal motion (Fig. 3) In each case there was a discrete, early systolic anterior septal notch 78 to 155 msec. in duration and unrelated to subsequent systolic septal motion. This notch was reproducible in each cardiac cycle. Approximately 70 to 80 msec. after the initiation of the QRS complex, the entire septum was noted to move rapidly 2 to 7 millimeters in an anterior direction then promptly return to its initial position. Following this early systolic anterior septal notch, septal motion continued during systole in a normal, paradoxical, or flattened pattern. This early systolic notch seen in patients with postoperative right bundle branch block is morphologically and temporally distinguishable from the

Table II Summary of clinical, electrocardiographic and echocardiographic data of 25 patients with postoperative right bundle branch block—Group III

Patient	Diagnosis	Age (yrs)	Time interval (months)	QRS		RR (sec.)	Notch characteristics			SM	Surgery
				Axis	Duration (sec.)		NH mm.	QN msec.	ND msec.		
Group A											
1	TOF	15	34	+ 70	.16	70	7.2	85	155	N	V,P I
2	TOF	10	57	+ 60	14	.87	3.3	79	134	N	V P,I O
3	TOF	12	76	+ 90	13	.55	2.7	71	109	N	V,P I
4	TOF	1.5	3	+150	12	43	4.0	70	98	F	V,P,I,O
5	PS	8	50	+120	12	.89	2.3	75	100	PD	V,I
6	TOF	8	30	+ 60	12	70	2.9	71	78	N	V,P,I,O
7	TOF	10	27	+ 0	15	1 10	3.2	–	112	N	V,P,I
8	TOF	8	57	– 10	15	.98	3 6	84	134	F	V,P,I,O
9	PA	10	25	+120	12	.84	3.4	75	98	N	V,P,I,C
10	TOF	16	57	+ 80	14	.83	4 6	90	146	F	V,P,I
11	TOF	5	10	+120	12	75	2.6	73	105	N	V,P,I
12	TOF	5.5	3	+135	13	.62	3.6	67	142	N	V,P,I
13	TOF	2.5	62	+135	15	77	3.4	70	114	PD	V,P,I
14	PS	5	55	+120	14	.69	4.2	70	104	F	V,I
15	TOF	4	15	+120	.12	.50	3.2	60	85	PD	V,P,I,O
16	PS	2	13	+210	14	.61	3.6	68	89	N	V,I
17	VSD	15	93	+230	.13	.80	5.8	78	128	N	V,P,I
18	TOF	10	62	+225	.15	75	3.4	68	104	N	V,P,I O
19	TOF	8	22	+255	13	.64	3.7	91	109	N	V,P,I
Group B											
20	TOF	8	31	– 45	.14	.61	3.1	97	122	N	V,P,I
21	TOF	17	42	– 45	14	.85	1.4	115	128	F	V,P,I
22	TOF	3	29	– 60	13	.60	1.2	70	83	F	V,P,I
23	PASD	14	60	– 50	14	78	2 0	82	67	PD	–
24	TOF	4	5	–120	.13	.66	2.9	69	82	N	V,P,I
25	VSD	12	47	– 30	12	.60	3.3	64	81	F	V,P

Abbreviations. C = conduit, F = flattened, I = infundibular resection; N = normal; ND = notch duration, NH = notch height, O = outflow patch, P = patched VSD; PA = pulmonary atresia with VSD; PASD = primum atrial septal defect, PD = paradoxical; PS = pulmonary stenosis, QN = Q-notch interval; RR = RR interval of two successive heart beats; SM = septal motion, TOF = tetralogy of Fallot; V = right ventriculotomy VSD = ventricular septal defect.

later notch related to the septal hinge point (Fig. 3A) and from the notch frequently seen in relation to the inscription of the P wave (Fig. 3B) The measurements of notch height, duration and the interval from the initial Q wave deflection for each patient are summarized in Table II

The mean notch height for the 19 patients in Group III A those patients with clockwise or figure-of-eight frontal plane QRS loops oriented between −10° to +?25 was 3.8 mm with a standard deviation of ±1 0 mm The mean notch height in Group III B six patients with counter clockwise frontal pl ne QR loops and frontal QRS axis of −30° to −130 3 ± 0 8 (Fig. 4) This difference w s st ally significant ($p < 0.05$).

There were no dif h QN interval and notch duration in both groups. The mean QN interval was 75 ± 8 msec. in Group III A and 83 ± 18 msec. in Group III B The mean notch duration was 113 ± 21 in Group III A and 97 ± 20 msec. in Group III B

There was no relationship between any of these three parameters and heart rate or QRS duration. The notch height was not related to subsequent systolic septal motion which was normal in 14 patients, flattened in seven, and paradoxical in four patients. No abnormalities of motion of the posterior left ventricular wall were detected.

The early systolic anterior septal notch was observed in each of the 25 patients with postoperative right bundle branch block pattern and was not seen in any patient with a normal QRS pattern.

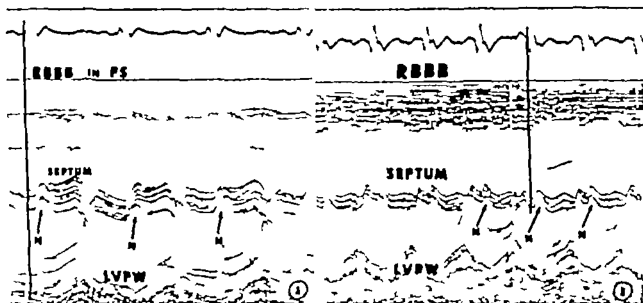


Fig. 3. A and B. Echocardiograms demonstrating the early systolic anterior septal notch associated with right bundle branch block *and its relation to other septal notches. A. Echocardiogram from patient operated on for* infundibular and valvular pulmonary stenosis demonstrating prominent early systolic anterior septal notch, *marked* \ and the previously described early diastolic notch. *B,* Echocardiogram showing an early systolic *anterior* septal notch following an earlier pre-systolic notch associated in time with P wave inscription.



Fig. 4. Echocardiogram from patient with counterclockwise frontal plane QRS loop. Note lower amplitude of the early systolic anterior septal notch (*identified by arrow*).

Discussion

Several new patterns of septal motion have been described since the initial echocardiographic description of septal motion in normal patients and those with right ventricular volume overload. Initial observations were limited to descriptions of abnormal patterns of septal motion associated with hemodynamic abnormalities. The description of unique septal motion patterns associated with left bundle branch block and Wolff-Parkinson-White syndrome, focused attention on the use of the echocardiogram to elucidate altered patterns of cardiac motion resulting from abnormal conduction sequences.

Normal septal motion has been previously well described. Immediately *after the P wave,* the posterior septal echo *moves anteriorly toward* the chest wall. This motion characteristically contin

ues until 0.04 to 0.06 sec. after the onset of the QRS when the direction is reversed, and the septum moves posteriorly away from the chest wall. This posterior motion reaches its maximal excursion before the peak of the T wave. From the latter point a small notch coinciding with the dicrotic notch of the carotid pulse tracing is noted just before the septal echo again moves anteriorly. This anterior motion continues or plateaus until the next P wave, which initiates the next cycle.

All 25 patients with postoperative right bundle branch block pattern showed a distinctive pattern of septal motion, strikingly different from the description of normal septal motion. In all 25 patients, whether the general pattern of septal motion was normal, paradoxical, or flattened, at a point 0 to 88 msec. after the initial QRS deflection, the entire septum was noted to move anteriorly during early systole then rapidly move posteriorly back to its initial position forming a short early systolic *anterior septal notch*. This notch was consistently recorded in each cardiac cycle and did not show any significant beat-to-beat variation. In addition, morphologically the notch did not vary significantly in a scan from the level of the posterior mitral valve leaflet to the cardiac apex. It has been previously shown that the pattern of septal motion may vary with the recording position from the level adjacent to the aortic root inferiorly to the mitral valve complex and the cardiac apex.

The patients in Group III were further subdivided into two groups, those with right bundle branch block pattern alone and those who also demonstrated left anterior hemiblock pattern. Although the QN interval and notch duration were not significantly different from patients with right bundle branch block pattern alone, the notch height was lower in patients with right bundle branch block and left anter r hemiblock pattern. It is possible that the omb ined effect of delayed condu tion in both the right bundle branch and th anterior fibers f th l ft bundle branch contribute to this decreased m gnitude of the early systoli anterior septal r n these patients.

An early systolic nterior septal t h uld not be demonstrated n any of h ntrol patients with a norma QRS complex r right entricular hypertrophy Patients in G up I had normall normal right heart hem d namics. The patients in Group II had significant right ventricular hypertension and electrocardiographic evidence of right ventricular hypertrophy without right ventricular conduction delay. These observations therefore indicate that the early systolic anterior septal notch is not present in normal hearts and furthermore is not related to the right ventricular hypertrophy present in patients of Group II. In addition, we have not seen this early septal notch in any of six patients who had open-heart surgery and subsequently showed normal QRS duration and configuration postoperatively. One of these patients had closure of a ventricular septal defect without ventriculotomy and the remainder had undergone aortic valvulotomy or replacement. Thus, the echocardiographic septal motion is unrelated to the open heart surgery per se.

The characteristic finding of an early systolic anterior septal notch in patients with postoperative right bundle branch block pattern is interesting for several reasons. First, this specific type of abnormal septal motion related to right bundle branch block pattern has not been previously described. It is distinctive from the patterns seen in patients with right ventricular volume overload,[8] conduction abnormalities such as left bundle branch block,[13-] Wolf Parkinson White syndrome (type B)[14-] and postoperative echocardiograms of patients with mitral and aortic valve surgery. Although the septum may move anteriorly during systole in these specific postoperative patients, the clear characteristic notch is not present. Secondly the notch appeared immediately after surgery and was found as late as 93 months thereafter consistent with the appearance and continued presence of the right bundle branch block pattern on the electrocardiogram. Since the mean interval following surgery was 38 months, these findings cannot be explained as acute changes in the early postoperative period similar in time to those found by Burggraf and Craige[2] in patients with mitral and aortic valve surgery. Finally the presence of the early notch was unrelated to the pattern of systolic septal motion whether paradoxical, flattened, or normal.

Because the early systolic anterior septal notch appeared in each patient postoperatively it may be suggested that surgery itself contributed to this abnormal septal motion. However in a different study by our group we have shown that a

similar abnormal early systolic anterior septal notch was present in each of 35 unoperated patients with and without congenital heart defects who demonstrated a right ventricular conduction delay on their electrocardiograms.[12] This information further supports our observation that the early systolic anterior septal notch found in patients with postoperative right bundle branch block pattern is truly the result of an abnormal ventricular activation sequence and is not merely the result of surgical intervention. Furthermore, three patients in our study with infundibular and valvular pulmonary stenosis did not have a ventricular septal defect patch. Hence, it is unlikely that this pattern of septal motion is due to the presence of foreign patch material in the ventricular septum.

It is interesting to note that the septal notch following the Q wave of the electrocardiogram in patients with postoperative right bundle branch block pattern is similar in timing but opposite in direction to the posterior notch described in patients with left bundle branch block. Thus, in addition to the previously described echocardiographic manifestations of left bundle branch, our findings of a unique pattern of septal motion associated with postoperative right bundle branch block pattern indicate that intraventricular conduction defects in general affect septal motion.

Summary

Echocardiograms were performed on 25 patients with postoperative right bundle branch block pattern 3 to 93 months after surgery to assess the possible effects of abnormal cardiac excitation on septal motion. Each of the 25 patients demonstrated a unique pattern of septal motion characterized by the presence of an early systolic anterior septal notch, brief in duration and unrelated to subsequent systolic septal motion, right ventricular size, or surgical procedure. Beginning approximately 70 to 80 msec. after the initial QRS deflection, the septum abruptly moved anteriorly 2 to 7 mm. and then returned to a baseline position. The total duration of this abnormal septal motion lasted 78 to 155 msec. This echocardiographic pattern was not seen in any of 30 patients in two control groups. Twenty had a normal QRS pattern and ten demonstrated right ventricular hypertrophy. In addition, patients who underwent open heart surgery and had normal right ventricular conduction postoperatively did not show this echocardiographic pattern with either normal or paradoxical septal motion. This previously undescribed echocardiographic pattern demonstrates that septal motion is uniquely affected in patients with postoperative right bundle branch block pattern.

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Heparin therapy A randomized prospective study

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Although it is agreed that heparin is the drug of choice in the treatment of major thromboembolic disease, the optimal method of administering and controlling therapy is still under dispute.[1-10] This study was undertaken to determine (1) if continuous heparin administration is associated with a lower incidence of bleeding complications than is intermittent administration, and (2) if laboratory monitoring of heparin therapy helps to reduce bleeding complications.

Methods

From October 1976, to October 1978, 80 consecutive medical patients at Cleveland Metropolitan General Hospital requiring heparin therapy were treated by random assignment either to continuous or to intermittent intravenous heparin therapy Informed consent was obtained. Each patient was given an initial bolus of 5 000 to 10,000 units of heparin and then begun on either 1,000 units/hour via a constant infusion pump or 100 units/Kg. every 4 hours. Heparin dosages were subsequently regulated to keep the Lee-White Clotting Time (LWCT) between 25 and 35 minutes[1] (Normal LWCT 4 to 8 minutes). In those patients on intermittent therapy the LWCT was determined 15 to 30 minutes before a heparin dose.

Daily clotting times were obtained LWCTs were performed on the first 47 patients using a 2-syringe, 3-tube technique and a 37 C water bath. Whole Blood Clotting Times (WBCT) on the remaining 33 patients—16 in the intermittent and 17 in the continuous group—were monitored using a 2-syringe, 1 tube technique at room temperature. This 1 tube WBCT correlated closely with the LWCT (Fig. 1) The 1 tube WBCTs were converted to LWCTs using the conversion method plotted in Fig. 1.

Hematocrits and urine and stool tests for blood were obtained at least every 3 days. Intramuscular injections and aspirin were withheld.

Major bleeding complications were defined as those which prolonged hospitalization or required permanent discontinuation of heparin therapy or blood transfusions. All other bleeding complications were considered minor

Statistical analysis was performed using standard least squares linear regression methods and the Student s t test.[11]

Results

Characteristics of the patient groups are shown in Table I. No patient had undergone surgery within the 2 weeks preceding inclusion in this study No patient received intramuscular injections or aspirin. Other risk factors were relatively more frequent in the intermittent group, although this difference was not significant. All patients had blood urea nitrogen levels below 50 mg./dl. and normal baseline prothrombin times, partial thromboplastin times (PTT) and platelet counts.

Bleeding complications are noted in Table II. No deaths resulted from heparin therapy The mean age (59) and male/female ratio (9/11) of patients with bleeding complications were not significantly different from the mean age (54) and ratio (26/34) of those without bleeding complica

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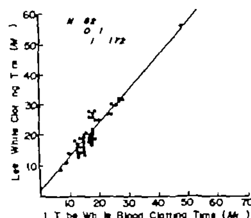


Fig. 1 Simultaneous determinations of the 1 tube whole blood clotting time (WBCT) and Lee-White clotting time in 23 patients on heparin therapy The 1-tube WBCT was used to monitor heparin therapy in 33 patients in this study

Table I Characteristics of the patient population

	Intermittent	*Continuous*
No. of patients	40	40
Mean age, yr (range)	56 (23-85)	55 (30-85)
Male/female ratio	18/22	17/23
Indications for heparin.		
Pulmonary embolus		
Suspected	8	7
Confirmed	22	20
Deep vein thrombosis	10	12
Arterial thrombosis		1
Mean days on heparin	7.83	9.55
Risk factors.		
Thoracentesis	9	2
Other trauma/vascular damage	1	1
LWCT > 35 mins. for 48 hrs	12	7
Any risk factor	18/40	10/40*

Difference not statistically significant.

Table II Bleeding complications†

	Intermittent	*Continuous*
Major bleeding		
Pulmonary hemorrhage		1T
Gastrointestinal	1S	
Wound hematoma	1T	
Severe hematuria	1S	
Intracranial bleeding (meningitis)		1T*
Hemothorax (post-thoracentesis)	1T	
Minor bleeding		
Gastrointestinal (occult)	2S	2S
Wound hematoma	1T*	1T*
Soft tissue	1S 1T* 1T	
Hematuria	1S 2S	
Hemorrhoidal	1T*	
Hemarthrosis (ruptured Baker cyst)	1T*	

Bleeding episodes which occurred at time when the LWCT was 35 minutes.
†Each complication is labeled as spontaneous (S) or related to trauma or vascular damage (T).

Table III Comparison of bleeding complication rates. Spontaneous bleeding complications are those not related to trauma, vascular damage, or a LWCT > 35 minutes.

	Intermittent	*Continuous*
Total bleeding complications		
Major	4/40 (10%)	2/40 (5%)
Minor	11/40 (28%)	3/40 (8%)†
Spontaneous bleeding complications		
Major	1/40 (3%)	0/40 (0%)
Minor	4/40 (10%)	2/40 (5%)

Difference not statistically significant.
†Difference significant to $P < 0.05$.

tions. Patients on continuous heparin received significantly less heparin (27 695 units/24 hours) than those on intermittent heparin (37 015/24 hours) ($P < 0.05$) However within each subgroup, the dosage of heparin given to patients with bleeding complications did not significantly differ from the dosage given to those without bleeding complications.

The LWCT was greater than 35 minutes on the day of bleeding in 50 per cent of all bleeding complications (Table II) Fifty per cent of all complications involved hemorrhage into areas of recent trauma or vascular damage (Table II) In only 35 per cent of bleeding complications was there no potential risk factor involved

At some time during the study 18 patients—six in the continuous and 12 in the intermittent group—required reduction in heparin dosage because their LWCT had been greater than 35 minutes for 2 consecutive days. Ten of these 18 patients (56 per cent) developed bleeding complications at the time their LWCTs were greater than 35 minutes. The incidence of bleeding in the remaining patients was 16 per cent ($P < 0.01$)

During the study 15 patients were at risk to bleed into areas of tissue trauma or vascular damage Eight of these patients (53 per cent) developed bleeding complications. The incidence of bleeding was 18 per cent in the 65 patients who were not at similar risk ($P < 0.02$)

to be the same in patients receiving intermittent as in those receiving continuous heparin therapy Thoracenteses, cut-downs, and other forms of soft tissue injury predispose to bleeding complications while laboratory monitoring with the LWCT may help to reduce bleeding complications.

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Table I Diagnostic categories

No heart disease		
Normal		19
Hypertension (without evidence of cardiac disease)		11
Minor T wave changes only		5
Left ventricular disease		
Atherosclerotic heart disease (without apparent right ventricular involvement)		59
Hypertensive cardiovascular disease (without apparent right ventricular involvement)		25
Valvular heart disease (without apparent right ventricular involvement):		17
Aortic stenosis	(8)	
Aortic insufficiency	(4)	
Mitral insufficiency	(2)	
Mitral valve prolapse	(1)	
Aortic insufficiency and aortic stenosis	(2)	
Primary left ventricular conduction disease		1
Right ventricular disease		
Cor pulmonale (without apparent left ventricular involvement)		6
Biventricular disease		
Primary myocardial disease		11
Valvular heart disease (with left and right ventricular involvement)		4
Pericarditis		1
Myxedema		1
Congenital heart disease (with left and right ventricular involvement)		1
Primary biventricular conduction disease (left anterior hemiblock and right bundle branch block)		1
Cor pulmonale (with additional left ventricular disease)		3

more PVC's on a routine twelve-lead electrocardiogram, (3) one or more PVC's recorded in V either on the twelve-lead electrocardiogram or on a subsequent rhythm strip of not more than ten minutes duration.

The data base for each study patient consisted of a thorough cardiovascular history and physical examination, chart review routine admission laboratory data and a recent chest x ray Data from cardiac catheterization and echocardiography were used when available.

Patients were classified into the following three categories, according to the ventricle of origin of the recorded PVC's (1) having only left ventricular PVC's (those PVC's with right bundle branch block pattern in Lead V) (2) having only right ventricular PVC's (those PVC s with left bundle branch block pattern in Lead V), (3) having both right and left ventricular PVC's (PVC's of both right bundle branch and left bundle branch block pattern in Lead V) Right bundle branch block pattern was diagnosed when there was a QRS duration of 12 sec. or more with a QR, RSR or RR pattern in Lead V [12]. Left bundle branch block pattern was diagnosed when there was a QRS duration of 12 sec. or more and a predominantly negative QRS complex with terminal S wave in Lead V_1 PVC's satisfying neither of these sets of morphologic criteria were considered to be of indeterminant morphology and were not included in this analysis. Only three patients were in this latter category

The presence or absence of heart disease was diagnosed using standard criteria. Included in the group with no heart disease were patients with only minor non specific ST and T wave changes on twelve-lead electrocardiogram and no other evidence of organic heart disease and patients with mild essential hypertension and absence of any evidence of cardiac involvement.

The patients with organic heart disease were further classified as to those having disease primarily affecting (1) the left ventricle (2) the right ventricle, or (3) both ventricles. The individual diagnosis in each category are listed in Table I. It is recognized that this classification is inexact. Disease of a single ventricle was considered to be present when the disease diagnosed was known to affect primarily that ventricle or when specific clinical or laboratory evidence indicated disease of only that ventricle. Disease of both ventricles was considered to be present when the disease diagnosed was one known to affect both ventricles or when two concomitant diseases were present, one affecting each ventricle or when specific clinical or laboratory evidence indicated disease of both ventricles.

The statistical significance of associations noted in the data was established by chi-square analysis of contingency tables. Tables larger than 2 × 2 were partitioned into 2 × 2 tables for further chi-square analysis, to more precisely define the significant associations.

Results

One hundred sixty five patients were included in the study with ages ranging from 19 to 88 years (mean of 61 years) There were 109 males and 56 females. Individual diagnosis and classification are presented in Table I. Thirty five patients had

no demonstrable organic heart disease. Twelve of these patients had normal echocardiograms, and one had normal left and right heart catheterization. One hundred thirty patients had organic heart disease. Twenty nine of these patients had abnormal echocardiograms and 71 had abnormal cardiac catheterization diagnostic of specific heart disease.

Sixty six patients had left ventricular PVC's, 71 had right ventricular PVC's, and 28 had both right and left ventricular PVC's.

Presence or absence of heart disease (Table II) Of the 35 patients with no heart disease six (17 per cent) had left ventricular PVC's, 26 (74 per cent) had right ventricular PVC's, and three (9 per cent) had both right and left ventricular PVC's. Of the 130 patients with heart disease 60 (46 per cent) had left ventricular PVC's, 45 (35 per cent) had right ventricular PVC's, and 25 (19 per cent) had both right and left ventricular PVC's. Patients with no heart disease had a significantly higher incidence of right ventricular PVC's ($p < .001$). Patients with heart disease had a higher incidence of left ventricular and of both right and left ventricular PVC's than patients with no heart disease ($p < .001$).

Left vs right ventricular disease (Table III) Of the 102 patients with left ventricular disease 52 (51 per cent) had left ventricular PVC's, 31 (30 per cent) had right ventricular PVC's, and 19 (19 per cent) had both right and left ventricular PVC's. Of the six patients with right ventricular disease one (17 per cent) had left ventricular PVC's, five (83 per cent) had right ventricular PVC's, and none had both right and left ventricular PVC's. Patients with left ventricular disease had a higher incidence of left ventricular and of both right and left ventricular PVC's compared to patients with right ventricular disease ($p < .05$). Patients with right ventricular disease had a significantly higher incidence of right ventricular PVC's than patients with left ventricular disease ($p < .05$).

Ventricle of origin of PVC (Table IV) Of the 66 patients with left ventricular PVC's, six (9 per cent) had no heart disease and 60 (91 per cent) had heart disease. Of the 71 right ventricular PVC patients, 26 (37 per cent) had no heart disease, and 45 (63 per cent) had heart disease. Of the 28 patients with PVC's arising in both ventricles, three (11 per cent) had no heart disease and 25 (89 per cent) had heart disease. Patients with left ventricular and biventricular PVC's had the same high incidence of heart disease while patients with right ventricular PVC's had a significantly higher incidence of no heart disease ($p < .001$).

Table II Presence or absence of heart disease

Patient	Ventricle of origin of PVC			Total
	Left (%)	Right (%)	Both (%)	
No heart disease	6 (17)	26 (74)	3 (9)	35
Heart disease	60 (46)	45 (35)	25 (19)	130
Total	66	71	28	165
$\chi^2 = 17.6$ ($p < 0.001$)				

Table III Left vs right ventricular disease

Patient	Ventricle of origin of PVC			Total
	Left (%)	Right (%)	Both (%)	
Left ventricular disease	52 (51)	31 (30)	19 (19)	102
Right ventricular disease	1 (17)	5 (83)	0 ( )	6
Total	53	36	19	108
$\chi^2 = 7.25$ ($p < 0.05$)				

Table IV Ventricle of origin of PVC

Patients	Presence or absence of heart disease		Total
	No heart disease (%)	Heart disease (%)	
Left ventricular PVC	6 (9)	60 (91)	66
Right ventricular PVC	26 (37)	45 (63)	71
Both	3 (11)	25 (89)	28
Total	35	130	165
$\chi^2 = 17.6$ (< 0.001)			

Discussion

The significance of ventricular extrasystole has intrigued the clinical cardiologist for a long time. Mackenzie in his book published in 1913 remarked that the presence of extrasystoles on the electrocardiogram should not be interpreted as a specific sign of injury to the heart. D Irsay in 1937 surveyed 100 cases of in hospital patients

with PVC's. Based on the results of this study he concluded that unifocal extrasystole could be detected on routine electrocardiograms in the absence of organic heart disease. In 1960 Hiss and associates[3] reported the incidence of PVC's in 67,375 asymptomatic and presumably healthy male Air Force personnel. Of the surveyed subjects, 419 (0.62 per cent) showed one or more PVC's.

Subsequent studies attempted to elucidate whether descriptive or measurable characteristics of PVC's such as morphology coupling interval, and QRS duration could discriminate between those PVC's that occur in healthy hearts and those detected in patients with organic heart disease.[4-6] In patients with PVC's and no heart disease the incidence of right ventricular PVC's was reported to vary from 60 to 96 per cent and the incidence of left ventricular PVC's varied from 4 to 33%.[3-6] In patients with PVC's and heart disease, previous studies reported a 73 to 83 per cent incidence of left ventricular PVC's and 18 to 27 per cent of right ventricular PVC's.[5] The incidence of multifocal PVC's in subjects without organic heart disease was reported to be extremely low.[5]

However the published data in regard to the relationship between site of origin of PVC's and presence or absence of organic heart disease has been difficult to interpret. These difficulties either related to the selection of patient population or to the classification of site of origin of PVC's.[3-6] The problems concerning patient selection related to the fact that in many of the previous studies patients were drawn from an unspecified population without explicit selection criteria[4] or were selected to have restricted diagnostic features. In many of the studies diagnostic criteria for the presence or absence of organic heart disease was unspecified. In regard to the site of origin of PVC's in previous studies, no criteria for assigning bundle branch block pattern were presented and patients with multifocal PVC's were excluded or classified according to the dominant morphology.[5]

The present study was designed to be as all inclusive as possible of subjects with PVC's. Electrocardiograms from all adult wards and services of a large general University Hospital and a large University affiliated Veterans Administration Hospital were screened for the presence of PVC's ensuring a cross-sectional population sample. Selection criteria were designed to exclude from study only those patients for whom too little data were available to allow reliable classification. Diagnoses were made by standard clinical and electrocardiographic criteria in addition these diagnoses were confirmed by echocardiographic examination and/or cardiac catheterization in 30 per cent of cases. All bundle branch block patterns were defined in Lead V to insure a uniform definition and a ten minute rhythm strip was allowed for recording a PVC in this lead. All data and conclusions were of proven statistical significance. In order that every patient have an adequate data base, it was felt necessary to restrict the study to hospital inpatients, a population with a higher incidence of heart disease than would be expected if outpatients were also included.

In patients with PVC's and no heart disease, the PVC's were of right ventricular origin in 74 per cent, of left ventricular origin in 17 per cent, and arising from both ventricles in 9 per cent. In patients with heart disease, the PVC's were of right ventricular origin in 35 per cent, of left ventricular in 46 per cent, and arising from both left and right ventricles in 19 per cent. This data revealed a significantly higher incidence of right ventricular PVC's in patients with no heart disease than in those with heart disease. It also showed a significantly higher incidence of left ventricular and of both right and left ventricular PVC's in patients with organic heart disease.

When patients with heart disease were subcategorized, it was seen that patients with right ventricular disease generally had right ventricular PVC's. In patients with left ventricular disease, the incidence of left ventricular and both right and left ventricular PVC's was much higher than in patients with right ventricular disease. This tendency for PVC's to arise from the diseased ventricle has not been previously reported. When examining the ventricle of origin of PVC's it was found that patients with left ventricular and both left and right ventricular PVC's were almost invariably found to have heart disease (91 per cent and 89 per cent, respectively). In patients with right ventricular PVC's, the incidence of patients with heart disease was greater than those without heart disease probably reflecting in part the high incidence of heart disease in the group of patients under study.

It is clear that when PVC's occur in the

presence of heart disease, they are likely to occur in the ventricle most affected by the disease process, which in advanced disease may be of both ventricles. The mechanisms by which myocardial disease alters the electrophysiological properties of myocardial tissue and induces PVC's is beyond the scope of this paper but such mechanisms should be operative in both ventricles. Thus, the ventricle most altered by disease would be the ventricle from which PVC's would originate. The reason for the predominance of right ventricular PVC's in the absence of organic heart disease is unclear. It is possible that these right ventricular PVC's reflect abnormality of the right ventricle that cannot be detected clinically or even with invasive cardiac catheterization studies.[4] In a previous study regarding ventricular tachycardia, we failed to demonstrate either anatomical or functional abnormality of either left or right ventricles in many patients with chronic recurrent right ventricular tachycardia.

The high incidence of right ventricular PVC's in patients with left ventricular disease may be explained in several ways. (1) The PVC's are not related to the presence of left ventricular disease but these patients had PVC's prior to the development of organic heart disease. (2) The PVC's reflect right ventricular disease that is clinically not detectable. (3) The PVC's have left bundle branch block morphology but are originating from the left ventricle.[10]

In summary our study suggests that recognition of the site of origin of PVC's can be of help to the clinician in the detection of organic heart disease. The presence of left ventricular or biventricular PVC's should raise the index of suspicion of the clinician for detection of left ventricular disease, suggesting the need for diagnostic cardiovascular work up. In patients with no apparent heart disease and right ventricular PVC's, additional investigation may not be necessary. However it must be noted that right ventricular PVC's may be seen with organic heart disease involving either the left or right ventricles.

Summary

One hundred and sixty five inpatients with premature ventricular contractions (PVC's) were clinically evaluated in regard to the presence (130 patients) or absence (35 patients) of organic heart disease. PVC's were classified based on QRS morphology (bundle branch block pattern) in Lead V_1 as being either left ventricular (66 patients) right ventricular (71 patients) or of both ventricles (28 patients). The incidence of organic heart disease was significantly greater in patients with left ventricular PVC's 60 of 66 (91 per cent) and biventricular PVC's 25 of 28 (89 per cent) than in patients with right ventricular PVC's 45 of 71 (63 per cent) ($p < 0.001$). Of the 130 patients with organic heart disease 60 (46 per cent) had left ventricular PVC's, 25 (19 per cent) had biventricular PVC's, and 45 (35 per cent) had right ventricular PVC's. Of the 35 patients without organic heart disease, six (17 per cent) had left ventricular PVC's, four (9 per cent) had biventricular PVC's, and 26 (74 per cent) had right ventricular PVC's.

These data suggest the following conclusions regarding inpatients with PVC's. (1) Organic heart disease is frequent in patients with right ventricular PVC's and almost universally present in patients with left ventricular and biventricular PVC's. (2) Patients without organic heart disease primarily have PVC's of right ventricular origin. The mechanism of the latter association is unknown.

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Rupture of the interventricular septum complicating myocardial infarction
Pathological analysis of 10 patients with clinically diagnosed perforations

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The development of interventricular septal defects within the necrotic myocardium of an infarct is a life-threatening but potentially correctable lesion. To examine the circumstances in which such myocardial ruptures occur the pathological findings in a group of patients with clinically diagnosed septal defects complicating myocardial infarcts were studied at autopsy after postmortem coronary arteriography. The results suggest that perforations of the interventricular septum tend to develop in large transmural first infarcts where coronary arteries adjacent to the occluded vessel also have significant obstructions.

Materials and methods

Patients autopsied at The Johns Hopkins Hospital were included in this study if (1) there was a clinically diagnosed ventricular septal defect complicating a myocardial infarct which was confirmed at autopsy and (2) the heart had been studied following postmortem coronary arteriography and formalin fixation in a distended state.

Hearts obtained at autopsy were given coronary artery injections with a barium gelatin pigment mass at 100 to 150 mm. Hg pressure. Following injection the intact heart was fixed overnight in a distended state by formalin introduced into the cavities at 30 to 40 cm. H_2O pressure while the heart was immersed in formalin. Following fixation stereoscopic radiographs were prepared of the intact heart and of the transverse sections into which it was sliced. The coronary arteries were transected at 2 to 3 mm. intervals and compared to the radiographs. Blocks of myocardium, at least 10 per heart, were removed for histological study from myocardial lesions, the area of septal perforation, and from other normal appearing areas. When myocardial necroses were encountered, any corresponding coronary artery lesions were sought and studied by serial histological sections. Blocks of the specialized conduction system containing sinoatrial node atrioventricular node and its branches, His bundle and proximal left and right bundle branches were removed and examined by serial histological sections using a standard method.

A curvature-thickness index (CTI) was determined for the right and left ventricular free walls and the interventricular septum as previously described. Briefly the curvature ($1/r$) of points in the mid wall of each of the three ventricular segments was determined in the transverse (TX) and apex-to-base (AB) planes from the postmortem radiographs. A plastic overlay with etched lines of known curvature was matched to the radiograph. The wall thickness (t) was measured at the point where the curvatures were measured. The index was determined for each segment by the formula, $CTI = t\,(1/r_{TX} + 1/r_{AB})$

Assessments of age, type, and extent of coronary artery and myocardial lesions were made

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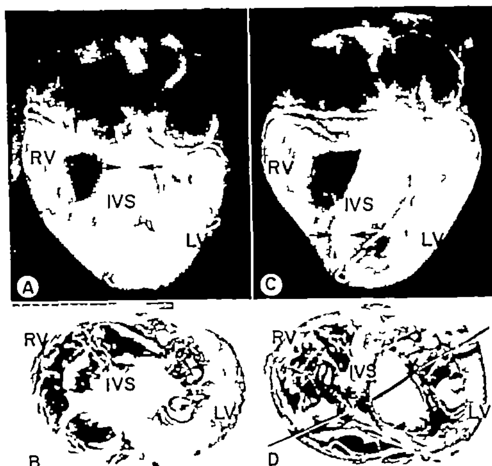


Fig 1 Comparison of inferior-basilar and mid-apical septal ruptures complicating myocardial infarcts. *A*, Postmortem coronary arteriogram of heart with an inferior-septal myocardial infarct produced by occlusion of the right coronary artery (*vertical arrow*). The infarct has septal perforation (*horizontal arrow*). Injection mass has extravasated into the defect and the left ventricular cavity The left coronary arterial tree shows significant obstructions *B* Transverse section of the ventricles at the level of the septal defect. The infarct involves the inferior wall of left (*LV*) and right (*RV*) ventricles and the inferior half of the interventricular septum (*IVS*). *C* Postmortem arteriogram of heart with an anterior-septal infarct caused by proximal occlusion of an unusually long left anterior descending coronary artery (LAD). The diagonal branch of the left and the right coronary arteries also have significant lesions The septal rupture is *at the arrows*. Compare the septal configuration to that shown in *A*. *D* Transverse sections of ventricles. The probe passes through the septal defect The infarct involves the entire septum and large part of the anterior wall of the left ventricle.

from gross and microscopic examination Infarct size was expressed as per cent of left ventricular surface area underlain by the infarct. The left ventricular surface area was calculated by measuring ventricular axes from the postmortem radiographs and considering the ventricle to be a prolate hemispheroid Infarct area was measured directly on the specimen and considered to be an ellipse. The clinical information autopsy findings, and results of pathological examination of the heart were then reviewed for each patient.

Results

Among the 1 130 adult (16 years of age and over) hearts studied after postmortem arteriography and fixation in distention there were 460 which had 768 pathologically demonstrated myocardial infarcts. The infarcts, defined as an area of myocardial necrosis or replacement fibrosis at least 3 cm in one dimension and in the distribution of a coronary artery with an occlusive lesion, were attributable to atherosclerotic coronary artery lesions in 692 instances, to coronary artery thromboemboli in 71 and to other coronary artery obstructions such as surgical ligation or arteritis in five. Ten patients had septal ruptures in myocardial infarcts demonstrated at autopsy which had been clinically diagnosed. Two other patients, not included in this study had septal ruptures produced by unsuccessful resuscitation efforts.

Table I Septal rupture after myocardial infarct—Clinical features

	Inferior-basilar rupture	*Mid-apical rupture*	*Total*
Number	6	4	10
Male:Female	4:2	4:0	8:2
Age (years)	70	61	66
	(58-82)	(51-75)	(51-82)
Infarct to rupture (days)	5	3	4
	(0.5-7)	(2-5)	(0.5-7)
Rupture to death (days)	3	14	8
	(0.5-9)	(0.5-52)	(1-52)
Recurrent pain	4 (67%)	1 (25%)	5 (50%)
Murmur	6 (100%)	4 (100%)	10 (100%)
Hypotension	6 (100%)	4 (100%)	10 (100%)
Congestive heart failure	1 (17%)	1 (25%)	2 (20%)
Shunt demonstrated	6 (100%)	2/2 (100%)	8/8 (100%)

Excludes one patient with operative closure of rupture who survived 100 days.

Clinical features

The ten patients with septal ruptures fell into two groups based on their morphological features, inferior basilar and mid apical defects (Fig. 1). The clinical features of the ruptures were similar both among the individual patients and in the two groups (Table I) and are considered together. The patients ranged in age from 51 to 82 years and eight were male. The interval from infarct to rupture varied from 0.5 to 7 days and averaged 4 days. Survival following rupture was one day or less in four patients, two days in two and three days in one. Two patients survived for 9 and 52 days post rupture. One patient who underwent operative closure of the defect lived for over 3 months thereafter.

Pain, which in retrospect appeared to coincide with the development of the ventricular septal defect, was noted in five (50 per cent). The pain was severe and sometimes episodic. It may have been present also in other patients who were transferred to this hospital following appearance of the defect. A murmur was noted in all patients, usually loud and holosystolic, and two patients had thrills. In eight instances the clinical impression of septal defect was confirmed by right heart catheterization. A step-up in oxygen saturation at the right ventricular level was detected.

Hypotension was present in every case and tended to increase in severity following onset of the septal rupture. In seven patients shock was the major cause of death. Symptoms or signs related to left-sided congestive heart failure were absent during the period immediately following rupture. In one case the pulmonary wedge pressure was 34 mm. Hg but pulmonary edema was not described. The two long-surviving patients developed left-sided heart failure but also had aneurysmal dilatation of the infarct which could have accounted for their pulmonary edema. Five patients were known to have hypertension, three had diabetes mellitus, and one had hypercholesterolemia.

Table II Septal rupture after myocardial infarct—Pathologic findings

	Inferior-basilar rupture	*Mid apical rupture*	*Normal hearts (4)*
Number of patients	6	4	17
Heart weight (grams)	525	545	319
	(390-690)	([illegible]0-650)	(227-420)
Coronary artery lesions:			
Location	RCA	LAD	—
Obstruction	5-100%	3-100%	
Obstruction	1 Recanalized	1 Recanalized	
Infarcts:			
Location	Transmural Inferior septal	Transmural Anterior septal	—
Size	26%	33%	—
	(2[illegible]-32)	(28-39)	
Number	6-first	3-first 1-third	—
Curvature-thickness indices			
Right ventricular free wall	0.36 ± 0.06*	0.36 ± 0.03*	0.20 ± 0.06
Interventricular septum	0.47 ± 0.16*†	0.14 ± 0.08*†	0.27 ± 0.06
Left ventricular free wall	0.83 ± 0.16	0.84 ± 0.07	0.81 ± 0.22

*Significantly different from normal ($p < 0.001$).
†Significantly different from each other ($p < 0.004$).

Pathologic findings

There were six patients in whom an inferior septal infarct was complicated by a rupture (Table II). In five of the six hearts the right coronary artery was totally occluded by fresh thrombus overlying ulcerated atherosclerotic plaques and in the other with long survival, there was recanalized thrombus. In each heart there were significant obstructions, greater than 75 per cent luminal narrowing, in those vessels which

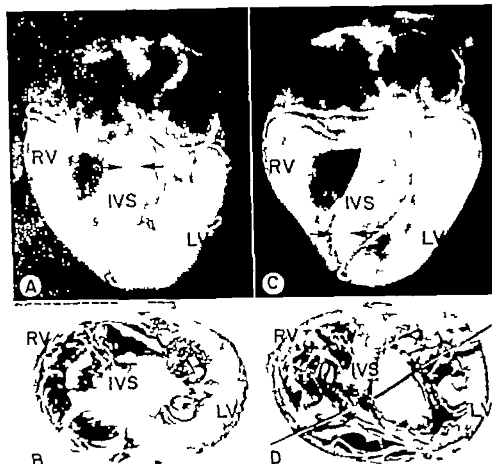


Fig. 1 Comparison of inferior-basilar and mid-apical septal ruptures complicating myocardial infarcts. *A* Postmortem coronary arteriogram of heart with an inferior-septal myocardial infarct produced by occlusion of the right coronary artery (*vertical arrow*). The infarct has septal perforation (*horizontal arrows*). Injection mass has extravasated into the defect and the left ventricular cavity. The left coronary arterial tree shows significant obstructions. *B* Transverse section of the ventricles at the level of the septal defect. The infarct involves the inferior wall of left (*LV*) and right (*RV*) ventricles and the inferior half of the interventricular septum (*IVS*). *C* Postmortem arteriogram of heart with an anterior-septal infarct caused by proximal occlusion of an unusually long left anterior descending coronary artery (LAD). The diagonal branch of the left and the right coronary arteries also have significant lesions. The septal rupture is *at the arrows*. Compare the septal configuration to that shown in *A*. *D* Transverse sections of ventricles. The probe passes through the septal defect. The infarct involves the entire septum and a large part of the anterior wall of the left ventricle.

from gross and microscopic examination. Infarct size was expressed as per cent of left ventricular surface area underlain by the infarct. The left ventricular surface area was calculated by measuring ventricular axes from the postmortem radiographs and considering the ventricle to be a prolate hemispheroid. Infarct area was measured directly on the specimen and considered to be an ellipse. The clinical information, autopsy findings, and results of pathological examination of the heart were then reviewed for each patient.

Results

Among the 1,130 adult (16 years of age and over) hearts studied after postmortem arteriography and fixation in distention there were 460 which had 768 pathologically demonstrated myocardial infarcts. The infarcts, defined as an area of myocardial necrosis or replacement fibrosis at least 3 cm. in one dimension and in the distribution of a coronary artery with an occlusive lesion were attributable to atherosclerotic coronary artery lesions in 692 instances, to coronary artery thromboemboli in 71 and to other coronary artery obstructions such as surgical ligation or arteritis in five. Ten patients had septal ruptures in myocardial infarcts demonstrated at autopsy which had been clinically diagnosed. Two other patients, not included in this study had septal ruptures produced by unsuccessful resuscitation efforts.

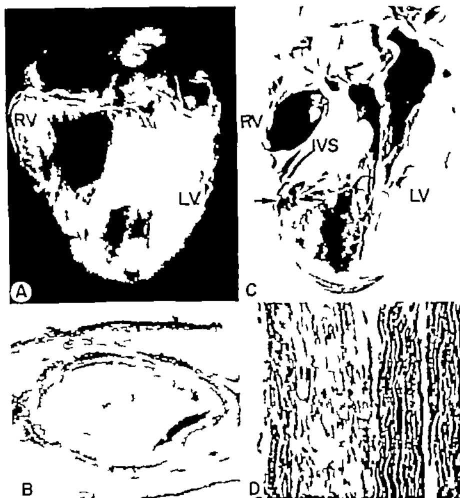


Fig. 3. Anterior-septal infarct caused by occlusion of the left anterior descending coronary artery complicated by mid-apical septal rupture. *A*, Postmortem coronary arteriogram with proximal occlusion of long LAD. The right and left diagonal coronary arteries ha significant lesions. The septum has convex to the left curvature in its basilar portion and perforation (*arrows*) in the infarcted apical portion. *B*, Occlusiv thrombus in the lumen of the LAD (Hematoxylin and eosin, original magnification ×16). *C*, Apex to base section of heart showing infarction of the apex and septal perforation (*arrow*). The basilar septum bulges into the left ventricular outflow tract. *D*, Endocardium and surviving subendocardial muscle (*left*) and infarcted myocardium with thin wavy fiber change on the right and subsiding acute inflammation consistent with the 5-day clinical age of the infarct (Hematoxylin and eosin, original magnification ×250).

to the apical portion of the septum would have been poor in all of the hearts. Two hearts had exceptionally long LAD arteries which extended halfway up the posterior interventricular groove and thus supplied the entire apical half of the septum. In the other two hearts significant obstructions were present in both the right coronary arteries and LAD diagonal branches. One of these latter two hearts had small subendocardial infarcts in the right and diagonal coronary artery distributions. All of the other nine hearts in the study had only the one infarct that was complicated by septal rupture.

All four of the anterior-septal infarcts were transmural and involved on the average 33 per cent of the left ventricular surface area. Coagulation necrosis predominated in the necrotic myocardium with only trivial amounts of contraction band necrosis on the infarct margins. The septal defects were in the mid-apical portion of the septum in the approximate center of the myocardial infarct and ranged in size from 0.75 to 1.5 cm. in diameter.

Configuration of the interventricular septum. A curious feature of the two groups of cases was that within each group the interventricular

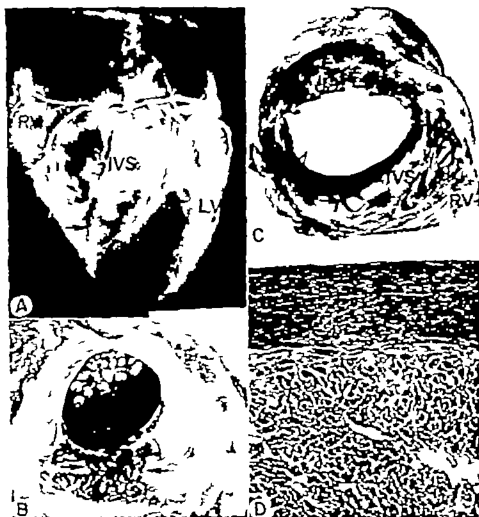


Fig. 4. The patient survived for 52 days following development of mid-apical septal perforation in an anterior-septal myocardial infarct. *A*, Postmortem coronary arteriogram with recanalized proximal occlusion of an unusually long LAD coronary artery. The basilar septum is convex toward the left ventricular outflow tract and the apical septum has healed infarct with central perforation (*lower arrow*). The infarct has undergone aneurysmal dilatation. *B*, Transverse section of the recanalized organizing thrombus overlying an ulcerated atherosclerotic plaque in the LAD. The ends of the ruptured fibrous cap of the plaque are shown by the arrows. (Verhoeff-van Gieson elastic stain, original magnification ×30). *C*, Transverse section of the ventricles viewed from the apical aspect. The healed transmural infarct involves the entire septum and the anterior left ventricle. The margins of the septal perforation are healed. *D*, The endocardium from an area adjacent to the septal defect shows well developed endocardial fibroelastosis *at the top*, surviving subendocardial muscle is *in the middle* and the replacement fibrosis of the healed infarct is *at the bottom*. The histologic features are consistent with the clinical age of the infarct (Verhoeff-van Gieson elastic stain, original magnification ×100).

septum (IVS) had a distinctive contour. In those hearts with anterior-septal infarcts and mid-apical ruptures the septum had its usual concave to the left curvature in the transverse plane. However in the apex-to-base plane the septum was convex to the left, the reverse of the normal curvature, and produced bulging of the basilar septum into the left ventricular outflow tract. In the hearts with inferior septal infarcts and inferior-basilar ruptures the septum was of the normal configuration but its curvature was greater than normal.

Comparison of the curvature-thickness indices for the right and left ventricular free wall and IVS with the same determinations from a group of normal hearts prepared and studied in the same manner showed highly significant differences for right ventricle and septum. The septal indices are also significantly different for the two infarct groups. The right ventricular free wall

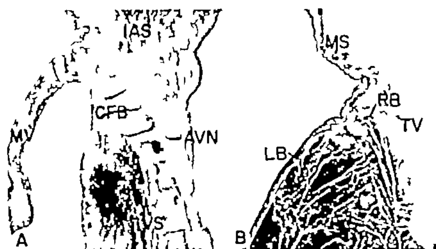


Fig. 5. *A*, Histological section of conducting system from patient with an inferior-septal infarct and inferior-basilar rupture. The necrosis extends to the top of the interventricular septum (*IVS*) adjacent to the central fibrous body (*CFB*). The atrioventricular node (*AVN*) and interatrial septum (*IAS*) show no necrosis. *MV* = mitral valve. *B*, Patient with an anterior-septal infarct and mid-apical septal rupture. The interventricular septum at this basilar level and the specialized conducting system including the atrioventricular node, His bundle, and proximal right (*RB*) and left (*LB*) bundle branches show no necrosis. *MS* = membranous septum. (Both Hematoxylin and eosin, original magnification ×10).

indices were significantly greater than normal in both groups of hearts with infarcts, probably secondary to the volume overload induced by the rupture. The left ventricular free wall indices showed no significant differences.

Correlation of electrocardiograms and conduction system studies. There was no specific pattern of electrocardiographic changes that characterized these patients. In each instance the position of the original infarct was detected on the initial electrocardiogram. Histologic study of the conducting system showed normal sinoatrial nodes in all patients. There was no interruption or necrosis of the atrioventricular node or its approaches, the His bundle or proximal left or right bundle branches in any patient. In the six patients with inferior septal infarcts the septal necrosis did not extend far enough anteriorly to involve the myocardium adjacent to the bundle branches (Fig. 5). Despite the presence of occlusion of the right coronary artery with potential ischemia of the atrioventricular node, none showed necrosis. One patient had a terminal widening of QRS complexes and one other had a 2:1 AV block.

In the patients with anterior-septal infarcts the bundle branches passed adjacent to the infarcted myocardium of the septum. The conducting fibers themselves did not show necrosis, probably because of their proximity to the blood within the ventricular cavity. Of the four patients with anterior-septal infarcts one had terminal bradycardia, one developed complete heart block, and a third had left anterior hemiblock and right bundle branch block. As noted, these conduction disturbances were apparently explained by ischemic destruction of the working myocardium itself rather than the specialized conduction system.

Discussion

The study shows that patients who develop septal rupture as a complication of myocardial infarction commonly have pain during the period when the defect is developing. If the pain arises from the site of perforation it is probably originating within the surviving endocardial or immediately subendocardial tissues, since the remainder of the wall is necrotic. With creation of the defect a murmur usually loud and holosystolic, is present and frequently a thrill as well. All of the patients developed hypotension which was usually severe and progressive. Left-sided congestive heart failure was absent in the immediate post rupture period and when it appeared later was explainable by aneurysmal dilatation of the left ventricle. Diagnosis of septal defect was established or confirmed in the eight patients studied

by right heart catheterization demonstration of an oxygen step-up in the right ventricle.

Pathologic studies showed two patterns of septal rupture. Six patients had right coronary artery occlusions with inferior-septal infarcts and inferior basilar defects. The other four patients had occlusions of the left anterior descending coronary artery producing anterior-septal infarcts and mid apical ruptures. In all 10 hearts the infarcts were large and transmural and in nine they were the only infarct. The pattern of coronary artery disease was such that possible collateral blood flow to the ischemic zone was inhibited by significant obstructions in the major adjacent arteries. Consistent with this is the observation that the infarcts had mainly coagulation necrosis. Contraction band necrosis, the development of which is dependent on reflow into transiently ischemic areas, was trivial and confined to the margins of the infarcts.

The factors mentioned, transmural necrosis and poor or absent collateral flow must be of importance in the pathogenesis of the septal rupture. Another potentially significant factor is the distinctive configuration of the interventricular septum in the two groups of cases. The curvature-thickness indices (CTI) of the three components of the ventricular walls correlate with the pressure producing capacity of the wall segment. In the hearts with inferior basilar ruptures the septal CTI s, determined at points not involved by the infarct, were significantly greater than those seen in normal hearts. It is possible that greater than usual curvatures in these septa may have contributed to perforation of their necrotic portions In contrast, the hearts with anterior-septal infarcts had septal CTI s significantly less than those seen in normal hearts. Examination of the radiographs showed an unusual distortion of the normal septal configuration with the apex to base contour reversed so as to be convex toward the left ventricle rather than the usual concavity. This reversal of contour is probably attributable to the fact that the entire apical portion of septum is involved in the infarct. The appearance of the left ventricle suggests that an element of subaortic outflow obstruction may have been introduced by the altered geometry. If true the consequent elevation of intracavitary pressure may have contributed to these mid apical perforations.

Septal perforation is a relatively uncommon complication of myocardial infarcts. The 1.3 per cent of infarcts with rupture observed here is similar to the experience of others.[4] Occurrence of the complication may be suspected from the development of a new murmur with concomitant hypoperfusion. The slight or absent early congestive failure seen in these patients may be a useful sign in distinguishing septal perforation from ruptured papillary muscle. Diagnosis may be established by right heart catheterization or by echocardiography

Surgical treatment of septal rupture is feasible. Current reports have emphasized the desirability of early operation in these clinically unstable and usually worsening patients.[3, 11] Coles and colleagues have noted the importance of distinguishing high and low defects, corresponding to the inferior basilar and mid apical of this report, because of the differences in surgical approach.

The sparing of specialized conducting tissues noted in these patients is in contrast to James experience[13] with five patients with posterior infarcts, all of whom showed necrosis in the atrioventricular node. It is indeed surprising that the six patients in this study with right coronary artery occlusions and large transmural inferior septal infarcts would not have shown more clinical evidence of atrioventricular node ischemia. Instead, among the four patients with anterior septal infarcts one had complete heart block and another developed left anterior hemiblock and right bundle branch block. These disturbances appeared to be explained by destruction of the working myocardium rather than by necrosis of the conducting fibers themselves.

The patients studied here show a uniform pathologic picture in that septal perforations complicate large transmural infarcts produced by total coronary artery occlusion and there is little opportunity for development of collateral blood flow. Two morphologic types of septal rupture are seen. An inferior basilar defect with right coronary occlusion and inferior-septal infarcts and a mid apical defect with left anterior descending occlusion and an anterior-septal infarct. A subsidiary factor leading to the septal defect may be the configuration of the interventricular septum. With inferior basilar defects the septum has greater than normal curvature suggesting poss

ble increased tension in the infarcted portion. Mid-apical ruptures are associated with a left ward convexity of the basilar septum causing it to protrude into the outflow tract. Any outflow tract obstruction could produce rupture of the apical septum by increased intracavitary pressure. Since the defects usually occur several days after infarction survival for a few more days brings the patient to a period when reparative reactions have begun in the area of the infarct. The onset of the healing process by this time suggests that surgical intervention would be technically possible. The severe life-threatening hypotension found in these patients is in accord with clinical studies suggesting treatment by early operative intervention.

Summary

Among 768 myocardial infarcts in 480 hearts studied after postmortem coronary arteriography and formalin fixation in a distended state, there were 10 infarcts (1.3 per cent) complicated by perforation of the interventricular septum. Infarcts with rupture were large (average 28 per cent of left ventricular surface area) transmural, usually first infarcts, produced by complete occlusion of a coronary artery and had little opportunity to receive collateral blood flow because of either significant obstructions of adjacent arteries or the pattern of coronary artery distribution. Six hearts had inferior-basilar defects in inferior-septal infarcts and four had mid-apical defects in anterior-septal infarcts. Development of septal rupture may relate to alterations of septal configuration more curved than normal with inferior basilar ruptures and bulging into the outflow tract with mid-apical ruptures. Pain was a common feature (50 per cent) of the development of the septal defect. A loud holosystolic murmur and severe hypotension were noted in all cases. Left-sided congestive heart failure was absent in the early post rupture period. Diagnosis was established by right heart catheterization in the eight patients studied. Post rupture survival without operation varied from 0.5 to 52 days (average 8 days) and the interval from infarct to rupture ranged from 0.5 to 7 days (average 4 days). The clinical course and pathologic findings in these patients support the desirability of early operative intervention in septal ruptures complicating infarcts.

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Hazards in treatment of systolic hypertension

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Elevated systolic blood pressure (SBP) has been shown to be associated with increased cardiovascular morbidity and mortality whether or not the diastolic blood pressure (DBP) values are also elevated. Systolic hypertension (HT) of arteriosclerotic origin has been defined as a separate entity the treatment of which is often encour aged but the outcome of such therapy is an unresolved issue.[2-4] Antiadrenergic drugs have generally proved non-satisfactory. The present study was carried out to investigate the effect of arteriolar vasodilation in the treatment of arteriosclerotic systolic hypertension, by using minox[illegible] potent direct vasodilator.

Materials and methods

Eight subjects whose blood pressure had been nonresponsive to a variety of antihypertensive agents entered the study fulfilling the following criteria:

1. SBP higher than 160 mm. Hg and DBP lower than 10[illegible] mm. Hg on all occasions during follow up of at least one year at our hypertension outpatient clinic despite therapy with a variety of drugs, including diuretics, hydralazine, methyl dopa and guanethidine.
2. Clinical evidence of atherosclerotic involvement of one or several organs (Table I).

All patients were given chlorthalidone 100 mg. daily or a thiazide diuretic in equivalent doses, and constant doses of beta blocking or other antiadrenergic agent (Table II) for at least two weeks, when minoxidil was added in small amounts. The dose of minoxidil was increased daily until a reduction of SBP of at least 25 mm. Hg was obtained or up to a maximum of 15 mg./24 hours. The respective dose was then kept constant for 20 days, unless severe adverse effects required earlier discontinuation of the drug.

The patients were seen daily or every other day during the first week of minoxidil administration and once or twice weekly during later follow up. Lying and standing blood pressure as well as standing pulse rate were recorded on each visit, according to a standard protocol. Serum creatinine, liver function tests, and electrocardiogram (ECG) were done weekly throughout the study.

Results

Table II summarizes the results obtained with minoxidil during an early stage of 2 to 5 days when the constant dose was reached, as well as at a later stage of 10 to 20 days. The constant daily dose of minoxidil ranged between 4 to 15 mg. (average 8.4 mg.) and the average duration of treatment was 49 days. The blood pressure of one patient was unresponsive at the maximal dose of 15 mg./day and his anginal pains became very severe on the nineteenth day of treatment. All the other patients had satisfactory reduction of SBP during the early stage and somewhat less so during the later stage. A significant increase in weight was observed after 10 to 20 days of treatment with minoxidil. In the four patients who received the drug for longer than 20 days, this

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Table 1 Summary of clinical data of patients with arteriosclerotic type systolic hypertension

Patient no.	*Age & sex*	*Known duration of HT (yrs)*	*Serum creatinine*	*Clinical manifest. of atherosclerosis*	*Abnormalities in the ECG*
1	61 M	9	1.3	PVD RAS	LVH
2	63 F	15	1.1	CVA	ST T
3	52 F	26	1.0	CVA	ST T
4	60 F	6	1.6	PVD	LVH + ST T
5	55 M	12	1.5	PVD	LVH
6	56 M	10	2.3	AP PVD	LVH + ST T
7	64 M	7	1.5	AP PVD	LVH + ST T
8	69 F	34	0.8	AP	LVH + ST T

Abbreviations: HT = hypertension, PVD = peripheral vascular disease; RAS = renal artery stenosis; CVA = cerebrovascular accident; AP = angina pectoris, LVH = left ventricular hypertrophy

could be overcome by more vigorous diuretic therapy leading to improved control of the blood pressure. The average standing pulse rate was 72.8/minute prior to minoxidil therapy and was not significantly affected by minoxidil either during the first 2 to 5 days or at 10 to 20 days (71.0 and 74.7 per minute, respectively). Serum creatinine and liver function tests were unaltered by minoxidil.

In seven patients minoxidil had to be discontinued because of severe adverse effects two patients developed preinfarction syndrome during the first week of minoxidil, one of them with severe ECG changes of anterolateral ischemia, one patient complained of marked aggravation of angina pectoris, severe dizzy spells and fainting sensation occurred in three patients; and two female patients developed very disturbing hypertrichosis.

Discussion

The management of systolic hypertension in general and especially that of arteriosclerotic origin is still an unresolved therapeutic challenge.[illegible] The increased rigidity of the great vessels is responsible for the disproportionately elevated SBP but the rise in peripheral resistance reported in this disorder[4] points to a concomitant involvement of the arterioles. Cardiac output is usually unchanged or decreased in elderly patients suffering from systolic hypertension. The fact that there are no means available to influence aortic and great vessel rigidity leaves us with the choice of reducing peripheral resistance by dilating the smaller arteries and arterioles. Attempts to do this by using antiadrenergic drugs have often failed, mainly because of a decrease in cerebral and/or myocardial perfusion, possibly due to further reduction of the cardiac output. It seemed logical, therefore to try to use a direct arteriolar vasodilator. Minoxidil is a recently developed agent in this category and it was chosen because of its high potency and almost universal effectiveness in reducing blood pressure.[illegible] However minoxidil was only being used as a way to lower SBP in order to test a hypothesis—not as a clinical trial of the drug in systolic hypertension, in which all patients would have received the same medications in the same sequence. Nor could the study be extended beyond the eight patients described above, because its continuation was considered unsafe after the development of coronary or cerebral ischemic phenomena in six of them. Had these patients not been followed closely and with extreme caution some may have been victims of major cardiovascular complications. The relatively small doses of antiadrenergic agents which were given to counteract reflex sympathetic stimulation were probably not responsible for any of the adverse effects, since such effects did not occur during their use in these patients prior to the administration of minoxidil. As to minoxidil itself in our previous experience we had not encountered any serious, unmanageable adverse effects in younger patients treated with this drug for up to several years.[14]

It is concluded that, although arteriolar vasodilation can effectively reduce blood pressure in systolic hypertension such a reduction by itself may be deleterious and therefore, contraindicated in patients with atherosclerosis involving vital organs. It is likely that perfusion to vital organs is compromised in such patients if their SBP is reduced even to or above normal values, no

Table II Results and adverse effects of minoxidil therapy

Patient no.	Before minoxidil		Minoxidil 2-5 day		Minoxidil 10-20 days	
	Supine BP*	Standing BP	Supine BP	Standing BP	Supine BP	Standing BP
1	202/68	190/86	154/84	162/90	1 6/94	170/90
2	210/90	1 8/86	158/72	156/"6	176/80	166/80
3	202/94	184/100	170/80	138/"8	172/84	160/74
4	228/100	218/98	138/70	140/78	180/88	170/90
5	186/82	166/86	152/78	166/88	188/94	164/68
6	228/98	212/94	230/108	166/88	214/94	186/"8
7	218/98	206/104	190/84	1"6/94		
8	194/74	184/64	130/54	120/52		
A erage	206.5/90.5	196 0/89.8	165.3/"8.8	155.5/80.0	184.3/89.0	172.7/83.3
p			.003/.031	.001/.021	.016/NS	.018/NS

Abbreviations: BP = blood pressure (mm Hg), D = diuretic; G = guanethidine; M = methyldopa, P = propranolol; S = spironolactone.

Table II Continued

Patient no	Weight			Maximal dose of minoxidil (mg.)	Additional medications (mg./day)	Adverse effects	Duration of minoxidil therapy (days)
	Before minox.	Minox. 2-5 d	Minox. 10-20 d				
1	64.5	64.5	65.5	4	D,P80	–	124
2	65 5	66.5	67.5	5	D,M500	Dizziness, fainting	11
3	50.0	49.5	50.5	12.5	D,S"5,P120	Hypertrichosis	46
4	63.0	63.5	66.5	6	D,P80	Hypertrichosis, fainting	130
5	66 0	68 0	68.0	10	D,G10	Famting	52
6	74.5	74 0	77.0	15	D,P240	Severe angina	19
	68.5	69.0		10	D,P60	Preinfarction syndrome	4
8	55 5	57.0		5	D,P60	Preinfarction syndrome	6
A erage	63 4	63 8	65.5	8 44			49
p		NS	032				

matter by what means. Therefore, as stated in a recent monograph, this entity requires thoughtful consideration and further study before being regarded as an indication for drug therapy

Summary

Eight patients with arteriosclerotic systolic hypertension whose blood pressure had been nonresponsive to conventional antihypertensive therapy were given minoxidil in daily doses of 4 to 15 mg. Within 2 to 5 days the blood pressure of seven patients was brought to more normal" levels. After 10 to 20 days of treatment a significant weight increase was observed with a concomitant rise of blood pressure which could be over come by more vigorous diureti therapy However six of the seven blood pressure responders and the one nonresponder omplained f severe adverse effects curtailing futher use of the drug. It is concluded that despite the effectiveness of arteriolar vasodilation in the reduction of elevated systolic blood pressure, such lowering may be deleterious in patients with atherosclerotic involvement of vital organs.

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The incidence and pattern of angina prior to acute myocardial infarction. A study of 577 cases

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One of the major goals in the management of patients with coronary artery disease is the anticipation and prevention of acute myocardial infarction. In this regard, it has long been known that many patients who develop acute myocardial infarction experience premonitory symptoms in the days and weeks prior to the actual event.[1-] Recognition of these symptoms before the onset of infarction might allow earlier hospitalization and institution of therapy designed either to prevent or to ameliorate the complications of acute myocardial infarction. Of the prodromal symptoms, ischemic chest pain is the most frequent and the easiest to assess. In particular a pattern of new onset or worsening angina is often regarded as a sign of impending infarction. The purpose of this study is to determine the incidence and pattern of angina as a premonitory symptom of acute myocardial infarction and to relate this symptom to the patient's prior history and subsequent hospital course.

Description of study

All patients admitted to the Myocardial Infarction Research or Ischemic SCOR units of the Massachusetts General Hospital during a period from January 1969 to December 1975 with a definite acute myocardial infarction were included in the study. Over this time there were 1,187 admissions, of whom 577 sustained a definite acute myocardial infarction. The diagnosis of acute myocardial infarction was based on the presence of at least two of the following criteria: a compatible clinical history, characteristic electrocardiographic changes, and an increase in appropriate serum enzyme levels.

In all cases patients were specifically questioned shortly after admission about ischemic chest pain in the month prior to the onset of infarction. The information thus obtained was stored on a specially designed form suitable for subsequent computer analysis. The design of the form allowed for the coding of symptoms as follows: no angina prior to infarction, chronic stable angina, chronic angina with worsening of symptoms in the month prior to infarction, and new onset angina in the month prior to infarction. The diagnosis of angina was based on the clinical opinion of the admitting physician guided by W.H.O. criteria. For the purpose of this study the following definitions were used.

Chronic Angina was defined as angina present for more than 1 month prior to the infarction. Patients without a clear history of angina who had had isolated episodes of chest pain prior to the month preceding the infarction were not regarded as having chronic angina.

New Onset Angina was defined as the new development of ischemic chest pain in the month prior to infarction. Patients with isolated episodes of ischemic pain occurring within this period of

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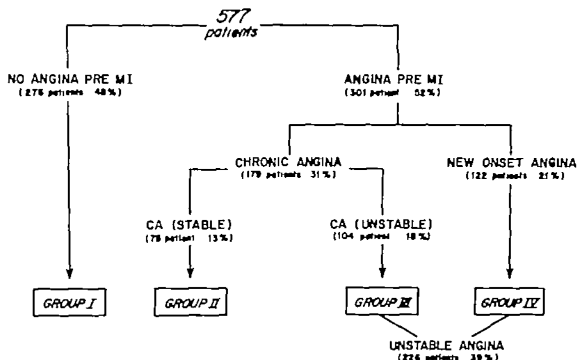


Fig. 1 Flow diagram indicating the breakdown of the 577 patients into the four subgroups.

Table I Characteristics of patients in the four groups and relationships to prior infarction, site of present infarction, and hospital mortality rate

	No. of patients	*Mean age*	*Sex*		*No. of patients with previous infarction*	*Site of present infarction*			*Hospital mortality rate*
			M	*F*		*Anterior*	*Inferior*	*Sub.End.*	
Group I (No angina)	276	57	220	56	34 (12%)	129 (47%)	121 (44%)	26 (9%)	33 (12%)
Group II (Chronic stable angina)	75	60	64	11	[illegible]	31 (41%)	30 (40%)	14 (19%)	15 (20%)
Group III (Chronic angina with increase in severity) ↕ "unstable" ↕	104	60	82	22	51 (49%)	48 (46%)	33 (32%)	23 (22%)	15 (14%)
Group IV (New onset angina)	122	59	98	24	32 (26%)	60 (49%)	44 (36%)	18 (15%)	15 (12%)

Abbreviations Sub End. = subendocardial infarction

time were regarded as having new onset angina.

Unstable Angina was defined as either new onset angina or an increase in severity of symptoms in patients with chronic angina in the month prior to infarction.

In addition to the information obtained from the computer the hospital records of all patients with angina were reviewed so that a more detailed assessment of the pattern and time course of the angina could be obtained.

The results were analysed using the Chi-square test for contingency tables.

Results

Patients were divided into four groups according to the presence or absence of preceding angina and also according to the type of angina. A flow sheet diagramming the various prodromes is shown in Fig. 1

Incidence of angina Two hundred and

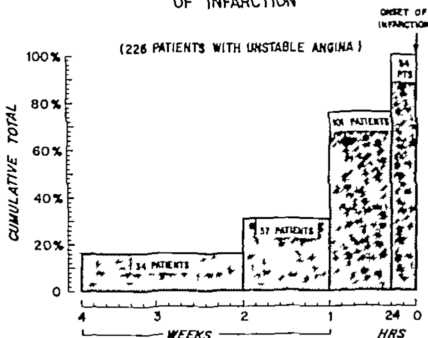


Fig. 2. Diagram indicating the period of time over which the 226 patients with new onset angina or prior chronic angina became unstable. As can be seen, 155 patients became unstable in period of 1 week or less.

seventy-six patients (48 per cent) had no angina prior to infarction (Group I) and the remaining 301 patients (52 per cent) had a history of angina in the month prior to infarction. One hundred and seventy nine of these patients had a history of chronic angina and of those, 75 (Group II) had no change in the pattern of angina prior to infarction, while 104 (Group III) described worsening pain in the month prior to infarction. One hundred and twenty two patients (Group IV) had new onset angina in the month prior to infarction. The total number of patients with unstable angina prior to infarction (Group III and Group IV) was 226 and this represented 39 per cent of the total series and 5 per cent of all patients with angina prior to infarction. The mean age, sex distribution, site of infarction and hospital mortality rate for each group are shown in Table I.

Time interval for onset of symptoms to infarction. The time interval between the onset of symptoms and the occurrence of myocardial infarction for the 226 patients with premonitory unstable angina is shown in Fig. 2. Thirty four patients developed unstable angina for between 2 to 4 weeks prior to infarction. Thirty seven patients developed unstable angina for between 1 to 2 weeks before infarction while 101 patients developed symptoms between 1 to 7 days from infarction. The remaining 54 patients developed symptoms of unstable angina within 24 hours of infarction. Thus, of those patients with unstable angina, the instability occurred within 1 week of infarction in 69 per cent.

Sex distribution. In the total series, there were 452 men and 115 women. Among the men the incidence of prodromal unstable angina was 39 per cent. It was 42 per cent among the women. This difference is not significant.

Age. The mean age of patients in the four groups is shown in Table I. Patients without a history of preceding angina (Group I) had a slightly lower mean age (57 years) compared to patients in the other three groups (60 years) but the difference was not significant.

Previous infarction. The incidence of previous infarction in each group is also shown in Table I. Patients with chronic angina (Groups II and III) were far more likely to have had a previous infarction than patients without preexisting angina (Group I and IV) (50 per cent incidence compared to 14 per cent). Patients in Group I had the lowest incidence of previous infarction (12 per cent). These differences were all statistically significant ($p < 0.01$).

Over-all 1?6 (27 per cent) of the 577 patients

had a past history of infarction and 83 (53 per cent) of these developed unstable angina prior to the present infarction, whereas 143 (34 per cent) of the 421 patients without a previous infarction developed prodromal chest pain. This difference, however did not apply to patients with pre-existing chronic angina. In these patients, the presence of a previous infarction did not increase the likelihood of developing unstable angina prior to further infarction. In contrast, in patients without chronic angina the incidence of premonitory chest pain was higher (49 per cent) in patients with previous infarction than in patients without previous infarction (23 per cent) This difference was statistically significant ($p < 0.05$).

Chronic angina. A history of pre-existing chronic angina correlated with the occurrence of prodromal unstable angina. In the total series 179 (31 per cent) of the patients had a history of chronic angina. Of these, 104 (58 per cent) developed unstable angina prior to infarction, whereas only 122 (31 per cent) of the 398 patients without pre-existing chronic angina (Groups I and IV) did so. This difference is highly significant ($p < 0.001$)

Electrocardiographic localization of infarction On the basis of standard electrocardiographic criteria, patients were classified as having one of three types of infarction. These were (1) transmural anterior wall infarction (including anterolateral and lateral infarction) (2) transmural inferior wall infarction (including inferolateral and true posterior wall infarction), and (3) subendocardial infarction. The incidence of the various types of infarction in each group is shown in Table I.

The location of the infarction differed between the groups. Patients with chronic angina were more likely to have a subendocardial infarction than patients without chronic angina. These differences were statistically significant ($p < 0.05$)

Hospital mortality rate The hospital mortality rate for each group is shown in Table I. Patients in Group II had a higher hospital mortality rate than patients in the other three groups. However this difference was not statistically significant. In those patients in whom both hospital and late follow-up data were available, there were 43 deaths among 387 patients without a previous myocardial infarct (12 per cent) compared with 35 deaths in 121 patients with prior infarction (29 per cent, $p < 0.01$).

Table II Incidence of prodromal chest pain as reported in previous studies

Authors	*No. of patients in series*	*Period of time over which prodromal symptoms were observed*	*Incidence of prodromal chest pain*
Yater et al. (1948)	60	3 weeks	10%
Mounsey[4] (1950)	139	3 months	29%
Wood[10] (1961)	100	3 months	43%
Kinlen (1969)	194	1 month	49%
Solomon et al. (1969)	100	2 months	59%
Stowers et al.[13] (1970)	198	2 months	55%
Fulton et al.[14] (1972)	121	2 months	44%
Alonzo et al. (1973)	160	2 months	67%

Discussion

The reported incidence of prodromal chest pain prior to myocardial infarction has ranged from 10 per cent[4] to 67 per cent with a wide range between these two values[1-] (see Table II) Many factors may account for this discrepancy including errors inherent in drawing conclusions from small numbers of patients, sampling from different populations, differences in diagnostic criteria, and variations in methods used to collect the information. In some studies the data have been derived by retrospective analysis of hospital records, while in others it has been collected prospectively by interviewing patients shortly after admission as was the case in this study In general, the incidence of prodromal chest pain has been highest when the data have been collected prospectively

In our study 52 per cent of patients had angina prior to myocardial infarction. If patients with stable chronic angina are excluded from this figure, then 39 per cent of our patients had unstable angina in the month prior to infarction. This figure, while similar to that observed by several other investigators,[1-] is significantly lower than that reported in some other recent studies.[12, 13] For example, in 1969 Solomon and co-workers[12] reported that *59 of 100 patients had* premonitory chest pain prior to the onset of infarction, in 1975 Stowers and Short[13] reported an incidence of 55 per cent, and Alonzo and

co-workers also reported an incidence of 67 per cent. In all these studies, prodromal symptoms were documented over a period of 2 months prior to infarction compared to the 1 month period of observation in our study. It is unlikely, however, that this could be the sole cause for variation in results. Another possible reason is that the characteristics of the populations studied may have been different. For example, in our study it was noted that patients with a past history of myocardial infarction were more likely to develop a prodromal pattern of unstable angina prior to further infarction than patients without such a history. Likewise patients with pre-existing angina were more likely to develop unstable angina prior to infarction than patients without pre-existing angina. It could be expected therefore that in populations with a high incidence of previous infarction or chronic angina, the incidence of premonitory chest pain will also be higher. The incidence of previous infarction is not mentioned in the studies of Solomon and associates and Alonzo and colleagues. It is of interest, however, that the incidence of pre-existing angina in the series reported by Solomon and associates was 41 per cent, which is higher than the incidence of 31 per cent in our series.

An interesting observation in this study was that patients with preceding unstable angina tended to develop their symptoms in close temporal relationship to the onset of actual infarction. Our results showed that 24 per cent of patients with unstable angina developed their symptoms within 24 hours of infarction and a further 45 per cent within 1 week of the infarction. Thus, even if these patients had immediately informed their physician of the presence of these symptoms, and even if hospital admission had been promptly arranged, in most cases little time would have been available to institute medical or surgical therapy. We encountered many instances where patients had not informed their physician of the development of unstable angina and few of the patients in this study were hospitalized prior to the onset of infarction. Similar observations have been made by other investigators. In the series of Stowers and Short only one-third of patients with prodromal symptoms consulted their physician prior to the onset of infarction. Alonzo and co-workers noted an even lower figure of [illegible] per cent. The conclusion to be drawn from these observations is that unless the public becomes better educated about prodromes of myocardial infarction, few patients with premonitory unstable angina are likely to be hospitalized prior to infarction.

The present study provides no information as to the incidence of subsequent myocardial infarction in patients who develop unstable angina. The reported incidence varies considerably with some estimates being as high as 41 per cent within three months while other estimates are much lower.[16, 4] Few prospective trials have been reported. In one such trial performed in Edinburgh by Fulton and co-workers, there was only a 14 per cent incidence of subsequent infarction in patients who presented with unstable angina over a mean observation period of 3 months. It seems, therefore, that while unstable angina commonly precedes acute myocardial infarction, most patients who present with unstable angina do not progress to infarction in the immediate future. The clinical relevance of these findings is that unstable angina can only be regarded as an insensitive and nonspecific guide to the risk of developing myocardial infarction in the near future.

The over-all incidence of chronic angina pectoris in this series was 31 per cent. This figure is comparable to earlier reports. Surprisingly only 68 per cent of these patients developed worsening of their symptoms in the month prior to infarction. Thus, even in this select group of patients, the development of unstable angina is a relatively insensitive predictor of the risk of subsequent infarction. This fact may be of clinical importance in the future if it can be shown that measures such as coronary artery surgery reduce the risk of future infarction in patients with chronic angina.

In this study it was noted that patients with preceding angina had a higher incidence of subendocardial infarction that those with new onset angina. Similar observations have been made by others.[11] A possible reason for this finding is that patients with chronic angina are likely to have a better developed collateral circulation than patients without angina and therefore the area of necrosis after coronary occlusion may be limited to the subendocardium.[14]

Almost half (48 per cent) of the patients in this series had no angina preceding their myocardial

infarction and only a small proportion of these patients (12 per cent) had a history of previous infarction. Thus for a large proportion of patients in the series, the present infarction was the first clinical manifestation of coronary artery disease. Until more sensitive screening methods to detect coronary artery disease are developed, anticipation of infarction in these patients without prodromal chest pain and without clinical evidence of coronary artery disease will always be difficult.

Summary

In order to determine the incidence and pattern of angina as a premonitory symptom of acute myocardial infarction, 577 consecutive patients with acute myocardial infarction were questioned shortly after hospital admission about the presence and pattern of chest pain prior to onset of infarction, with particular emphasis on the month prior to infarction. Two hundred and seventy six patients (48 per cent) had no angina before infarction (Group I) whereas 301 (52 per cent) did. One hundred and seventy-nine patients (31 per cent) had a history of chronic angina, and of these, 75 had no change in the pattern of angina prior to infarction (Group II) while 104 noticed worsening of their symptoms in the month prior to infarction (Group III). One hundred and twenty two patients (21 per cent) had new onset angina in the month prior to infarction (Group IV). The number of patients with unstable angina prior to infarction (Groups III and IV) was therefore 226 or 39 per cent of the total series. In patients with unstable angina, the increase in severity of symptoms or the development of new onset angina occurred within a period of 1 week or less in 69 per cent. Patients with a history of previous infarction or chronic angina had a higher incidence of unstable angina prior to infarction than patients without such a history ($p < 0.05$). Patients with prior angina (Groups II, III and IV) had a higher incidence of subendocardial infarction than patients without angina ($p < 0.05$). The hospital mortality rate in the four groups did not differ significantly.

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Relationship of atrial fibrillatory wave amplitude to left atrial size and etiology of heart disease

An old generalization re-examined

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It is widely accepted that the amplitude of the fibrillatory wave recorded in the electrocardiogram during atrial fibrillation correlates directly with the size of the left atrium and may predict the type of heart disease present. Coarse or high amplitude fibrillatory waves have been associated with rheumatic heart disease and large left atria, while in contrast fine or low amplitude fibrillatory waves have been thought to indicate the presence of atherosclerotic heart disease and normal left atrial dimensions.[1-4] In light of current techniques and changes in diagnostic criteria, re-evaluation of data supporting the relationship between fibrillatory wave size and etiologic diagnosis or left atrial size is necessary. Previous studies have used either roentgenographic, electrocardiographic, or hemodynamic factors to identify left atrial enlargement or disease. The reliability of echocardiography in determining left atrial size has been well established.

The purpose of the present study was to examine the relationship between the amplitude of fibrillatory waves recorded in the electrocardiogram during atrial fibrillation and (1) left atrial size as determined by echocardiography and (2) etiology of the cardiac disease.

Methods

Thirty-seven consecutive patients with chronic atrial fibrillation undergoing routine M mode echocardiography were studied. The cardiac diagnoses in the patients were rheumatic heart disease (17), coronary artery disease (5), hypertensive heart disease (6), cardiomyopathy (7), and two patients had no disease. Routine 12 lead electrocardiograms and V rhythm strips were obtained at standard speed and sensitivity. The amplitude of each fibrillatory wave in millimeters was measured in Lead V independently by two observers. The measurements were made from the upper edge of the trough to the upper edge of the peak by the method of Peter and colleagues. Both the average fibrillatory amplitude and the maximum amplitude (the largest single amplitude measured) were determined. Forty five to 70 fibrillatory waves were measured in each patient during a ten-second interval.

The size of the left atrium was assessed using end systolic left atrial internal dimension as determined with routine M mode echocardiography (normal value 40 mm. or less). The data were analyzed using a Student's paired t test.

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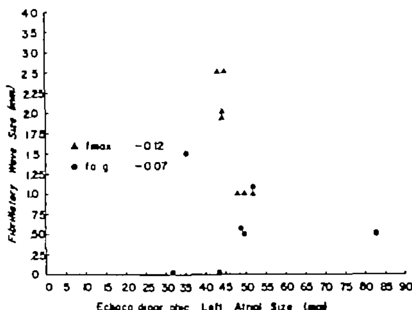


Fig. 1 Relationship of atrial fibrillatory wave size and echocardiographic left atrial size. *The triangles* denote the maximum fibrillatory wave amplitude *(f max)* and *the circles* represent the average of all fibrillatory waves *(f avg)* recorded in 10 seconds. The correlation coefficients *(r)* are indicated.

Results

No significant correlation was found between left atrial dimension and fibrillatory wave amplitude (Fig. 1). The correlation coefficients between these two parameters were −0.12 using maximum fibrillatory wave amplitude and −0.07 using average fibrillatory wave amplitude.

Of the 37 patients, 26 had left atrial dimensions greater than 40 mm., and in 14 of these, the average fibrillatory wave amplitude was less than 1 mm. Conversely, the remaining 11 patients with normal left atrial dimensions (40 mm. or less), had average fibrillatory wave amplitude ranging from 0 to 2.5 mm. (Table I). Furthermore, in the patient with the largest left atrial dimension (80 mm.) the average fibrillatory wave amplitude was only 0.5 mm. In the patients with the smallest left atrial dimensions (30 to 35 mm.) the average fibrillatory wave amplitudes ranged from 0 to 4.0 mm.

The etiology of heart disease was not significantly related to the fibrillatory wave amplitude (Table II). Only 53 per cent (9 of 17) of patients with rheumatic heart disease had fibrillatory wave size > 1 mm. Conversely more than half (10 of 18) of patients with fibrillatory wave size ≤ 1 mm. had non-rheumatic disease. In addition there was no significant change in these relationships if the fibrillatory wave data were analyzed in terms of categories such as "coarse" or "fine" rather than the numerical approach we employed.

Discussion

This study refutes the commonly held contention that the fibrillatory wave amplitude in atrial fibrillation is correlated with either left atrial size or the type of associated heart disease. In the past, various amplitude criteria have been utilized to categorize fibrillatory waves into either "fine" or "coarse."[1] In our study a quantitative analysis was performed based on actual amplitude. However dividing our patients into categories of fine or coarse fibrillatory waves using either a 0.5 or 1.0 mm. dividing point did not affect the statistical insignificance of the data.

Previous studies that have suggested a relationship between coarse fibrillatory waves and left atrial enlargement have utilized roentgenographic, operative, or autopsy studies as their primary methods to determine left atrial size. However these studies were biased by the preponderance of patients with rheumatic heart disease. This was necessary because left atrial size was determined at the time of cardiac surgery which at the time of the studies was only performed for rheumatic heart disease. The current use of echocardiography to determine left

Table I Relationship between left atrial and fibrillatory wave size

Left atrial size			
	Increased >40 mm.	14	12
	Normal ≤40 mm.	4	7
		≤1 mm.	>1 mm.
		Fibrillatory wave size	

Table II Relationship between etiology of heart disease and fibrillatory wave size

Rheumatic heart disease	8	9
Non-rheumatic heart disease	10	10
	≤1 mm.	>1 mm.
	Fibrillatory wave size	

*One normal patient in each group.

atrial dimension quantitatively would appear to be the more precise and reproducible method for these correlations.

While other authors have suggested that the amplitude of fibrillatory waves correlates well with the type of underlying heart disease,[1-4] our data (using echocardiography to determine left atrial size) do not support this contention. Although coarse fibrillatory waves may occur *somewhat more frequently* in rheumatic disease, the difference in frequency between rheumatic and non rheumatic diseases is too small to be of clinical usefulness.

Peter and co-workers[6] have observed a positive correlation between the fibrillatory wave amplitude and the subsequent p terminal force in Lead V of the electrocardiogram in patients following reversion to sinus rhythm. Recently we[8] have shown that intra atrial conduction time (from the onset of the P wave to the activation of the coronary sinus) was prolonged in most patients with an abnormal P terminal force in Lead V and that this intra atrial conduction defect did not correlate with either left atrial size, pulmonary capillary wedge pressure or type of heart disease. It is, therefore interesting to hypothesize that abnormalities of intra atrial conduction are responsible for the coarse fibrillatory wave morphology in atrial fibrillation. The relationship, however between coarse fibrillatory waves and the type of heart disease or size of the left atrium appears not to be established.

Summary

It is commonly stated that coarse f waves in atrial fibrillation suggest the presence of rheumatic heart disease and large left atrial size, whereas fine f waves indicate non-rheumatic disease and small left atrial size. Using echocardiography as a more reliable indicator of left atrial size, 37 consecutive patients with chronic atrial fibrillation were evaluated. The correlation coefficients between left atrial size and maximum f wave amplitude was −0.12 and −0.07 using average f wave amplitude. Only 53 per cent (9 of 17) of patients with rheumatic heart disease had f wave > 1 mm. and 56 per cent (10 of 18) of patients with f wave size ≤ 1 mm. had non rheumatic disease.

This study refutes the contention *that the f* wave amplitude in atrial fibrillation is correlated with either left atrial size or etiology of heart disease. It is possible that an intra-atrial conduction defect is responsible for coarse f wave morphology

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Noninvasively induced postextrasystolic potentiation of ischemic and infarcted myocardium in patients with coronary artery disease

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Echocardiography has proven useful in demonstrating abnormal left ventricular wall motion (asynergy) in patients with coronary artery disease (CAD). Recent angiographic–echocardiographic studies have shown a correlation between lesions of the left anterior descending artery (LAD) and reduced interventricular septal wall excursion,[1-4] and between lesions of the right coronary artery (RCA) and/or left circumflex artery (LCF) and reduced excursion of the posterior wall. These wall motion abnormalities are most frequent when the ECG also shows evidence of a transmural myocardial infarction in the region subserved by the stenosed vessel. One of the clinical questions that remains unanswered is wether such wall motion abnormalities—with or without corresponding Q waves—are due primarily to myocardial ischemia without extensive scar formation and thus potentially reversible, or are largely the result of scar formation and probably irreversible. Techniques are currently available to determine the reversibility of regional myocardial asynergy during left ventriculography These techniques include the use of a ventricular premature beat (VPB) to induce postextrasystolic potentiation (PESP) a potent inotropic stimulus in mammalian heart muscle, but until recently there has been no reliable method of inducing VPB s noninvasively and hence no comparable way of detecting contractile reserve during noninvasive evaluation of wall motion With the development of an external mechanical cardiac stimulator by Zoll and associates, however such studies are now possible. We have previously used this device to introduce VPB s noninvasively during echocardiography and evaluate *over-all* ventricular reserve in a variety of cardiac disease states. In the present study we use it to evaluate the effect of PESP on the reversibility of *localized* abnormalities of wall motion in patients with CAD

Materials and methods

Patient selection. Criteria for selection of CAD patients for this study included (1) angiographic evidence of significant coronary artery obstruction, i.e., greater than 75 per cent reduction in lumen diameter without concomitant valvular or congenital heart disease, (2) regular sinus rhythm without evidence of left bundle branch block, (3) technically adequate echocardiographic tracings of at least the basal septum and left ventricular posterior wall (and, whenever possible, the apex) with the patient lying supine or rotated slightly to the left. The 29 CAD patients who were studied ranged in age from 40 to 62 years. All patients gave informed consent for these studies. Four additional patients with chest pain syndromes

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Fig. 1 External mechanical cardiac stimulator positioned on patient precordium just lateral to the echocardiographic transducer.

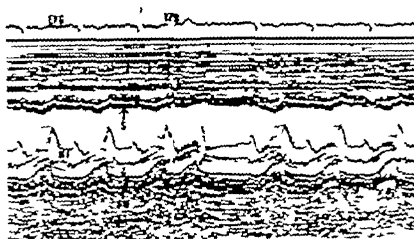


Fig. 2 Echocardiogram demonstrating augmentation of septal (*S*) and posterior wall (*PW*) motion following externally-induced ventricular premature beat (*VPB*). Although this patient had a prior inferior myocardial infarction, posterior wall excursion was normal in the control beat (9 mm.) and increased to 11 mm. following the VPB. Septal wall motion excursion was abnormal in the control beat (2 mm.), but increased to normal levels (4 mm.) following the VPB. There was no electrocardiographic evidence of anterior wall infarction. At coronary arteriography the patient demonstrated significant stenosis of the left anterior descending and right coronary arteries. *m.* = mitral valve apparatus, *EKG* = Lead II of the electrocardiogram.

and totally normal cardiac catheterization studies served as a control group.

Electrocardiography. Standard New York Heart Association electrocardiographic and vectorcardiographic criteria were used for defining transmural anteroseptal, inferior, and posterior myocardial infarctions.

Induction of premature ventricular beats. These procedures have been described in detail previously and have proven safe and reliable. Briefly, the VPBs were induced with the external mechanical stimulator positioned on the precordium, either at or near the point of maximum impulse but not over the nipple (Fig. 1). The stimulator was a modified stapling gun which was discharged manually after the T wave was observed on an oscilloscope. Stimuli were calibrated from 0 to 1.5 joules.

Echocardiographic procedures. Echocardiograms were recorded using M mode scans with the patients either supine or rotated slightly to the left (Fig. 2). A Smith Kline Instruments

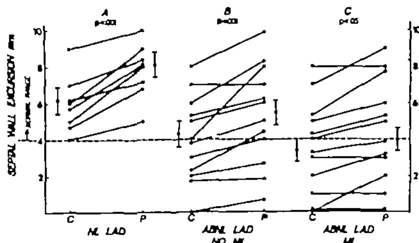


Fig. 2. Effect of postextrasystolic potentiation on septal wall excursion. Septal wall excursion is plotted in the control *(C)* and potentiated *(P)* beats in regions with normal *(NL)* left anterior descending *(LAD)* arteries *(panel A)*, stenosed *(ABNL)* LAD but no evidence of anterior wall myocardial infarction *(MI)* on ECG *(panel B)*, and stenosed LAD with ECG evidence of anterior wall MI *(panel C)*. The increase in septal wall excursion following postextrasystolic potentiation is significant in all three subgroups. Normal septal excursion is ≥ 4 mm.

Ekoline 20 System employing a 2.25 MHz transducer coupled to an Irex Continutrace 101 Multichannel Recorder was utilized for all studies. The transducer was placed in the standard position in the left fourth intercostal space lateral to the left sternal margin and an M-mode sweep was performed from the aortic root to the apex of the left ventricle. The site with the most pronounced asynergy was selected as the area of interest for evaluating the effect of PESP. A standard Lead II electrocardiogram was simultaneously recorded on the echocardiogram. Excursion of the left interventricular septum and posterior wall endocardium was measured from end-diastole (onset of QRS complex) to maximum posterior and anterior excursion, respectively, in beats preceding and following the VPB. Measurements were to the nearest millimeter. The lower limit of normal values in our laboratory for endocardial excursion for the interventricular septum and posterior wall are 4 mm. and 9 mm., respectively. A ratio of posterior wall to septal wall excursion was obtained by dividing the posterior wall excursion by the septal excursion, with a value of 2.5 or greater considered abnormal. Echocardiographic measurements were made within 24 hours of the cardiac catheterization and without knowledge of the results of coronary arteriography or left ventriculography (and vice versa).

Cardiac catheterization procedures. Selective coronary arteriograms were obtained in multiple views using either the Judkins or Sones techniques and recorded on 35 mm. film. The coronary arteriograms were analyzed without knowledge of the echocardiograms. Obstructive lesions were classified as significant if there was greater than 75 per cent narrowing of the lumen of the LAD, LCF, or RCA, or any of their major branches.

Technically adequate biplane cine left ventriculograms demonstrating the septal and posterolateral walls (in the left anterior oblique projection) were obtained in 15 patients (all with CAD) and seven of these included single ventricular premature beats of approximately the same R-VPB interval as that obtained during echocardiography. The VPB's were induced by methods described in detail previously. The septal and posterolateral radii of the major transverse diameter in this projection were measured in the beat preceding and the beat following the VPB. Normal shortening from end-diastole to end-systole is ≥ 20 per cent in our laboratory.

Results

In none of the patients in this series did serious complications (such as repetitive ventricular tachyarrhythmias or angina) occur following external mechanical stimulation, nor was there more than minimal chest wall discomfort. No premedication was necessary nor were analgesics required in any patient. No patient experienced more than five attempts at inducing VPB's. The interval between the R wave of the sinus beat and

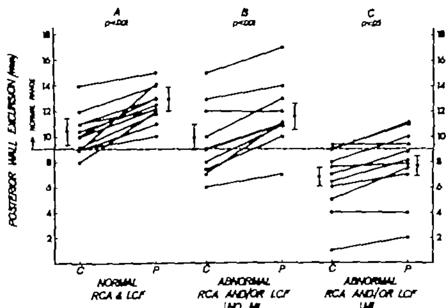


Fig. 4. Effect of postextrasystolic potentiation on posterior wall excursion. Same format as Fig. 3, except that *MI* refers to inferior and/or posterior myocardial infarction, *RCA* to right coronary artery and *LCF* to left circumflex artery. All three subgroups had significant increases in posterior wall excursion. Normal posterior wall excursion ≥ 9 mm.

the onset of the VPB induced by the mechanical stimulator averaged 486 msec. ± 20 (mean ± S.E.M.) and the range was 370 to 610 msec. Previous studies from our hospital demonstrated no significant changes in PESP in the same patient when coupling intervals within this range were compared.

1. Septal wall motion (Fig. 3)

A. *Relation between reduced septal wall excursion, LAD disease, and anteroseptal myocardial infarction.* Twenty-five patients had > 75 per cent obstruction of the LAD. Abnormal septal wall excursion could be demonstrated in 13 of the 25 patients (52 per cent) including six of the 12 patients *without* evidence of infarction and seven of the 13 patients with such findings. An abnormal posterior wall/septal wall excursion ratio was present in nine of the 13 patients with reduced septal wall excursion but in no patients with LAD lesions and normal septal wall excursion.

B. *Effect of PESP.* In all eight patients without significant LAD disease (four control subjects and four CAD patients, *panel A* of Fig. 3), there was increased excursion during PESP: 6.2 mm. ± 0.6 (mean ± S.E.M.) to 7.9 mm. ± 0.7, p < .001. In the 12 patients with LAD disease but no anteroseptal infarction (*panel B*) only two patients failed to increase their excursion and the group as a whole also demonstrated significantly increased excursion: 4.2 mm. ± 0.7 to 5.7 mm. ± 0.8, p < .001. Five patients in this subgroup did not have normal wall excursion at rest and two reached the normal range during PESP (an example is depicted in Fig. 2). In the 13 patients with prior infarctions (*panel C of Fig. 3*), five patients showed no change, but the group again showed a significant increase in excursion: 3.3 mm. ± 0.8 to 4.0 mm. ± 0.8, p < .05. Seven patients in this subgroup had abnormal wall excursion at rest and only one achieved normal excursion with PESP. *In none of the patients did an abnormal posterior wall to septal wall excursion ratio revert to normal.*

2. Posterior wall motion (Fig. 4)

A. *Relation between reduced posterior wall excursion, RCA and/or LC disease, and inferior or posterior myocardial infarction.* Twenty-one patients had either > 75 per cent stenosis of the RCA or LCF and 16 had disease of both vessels. Reduced posterior wall excursion was demonstrated in 12 of the 21 (60 per cent) including *four of 10 without evidence of infarction* and *eight of* 11 with evidence of infarction.

B. *Effect of PESP.* In all 12 patients without either RCA or LCF disease (four control subjects and eight CAD patients, panel A of Fig. 4), *there* was increased excursion during PESP: 10.4

*tical comparison by paired t test unless otherwise noted.

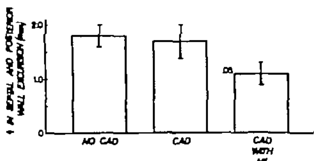


Fig. 5. Increase in wall excursion with postextrasystolic potentiation in relation to presence or absence of ECG evidence of myocardial infarction *(MI)*. Twenty regions without cornary artery disease *(CAD)* are compared to 22 regions with CAD but no myocardial infarction and 24 CAD regions with evidence of prior MI (see text). Increase in echocardiographic (ECHO) wall excursion with PESP was significantly less in the MI regions (1.1 ± 0.2) compared to either of the other two subgroups (1.6 ± 0.2 and 1.7 ± 0.3).

mm. ± 0.8 to 12.8 mm. ± 0.7 p < .001 *(panel A)*. In the 10 patients with RCA and/or LCF disease but no infarction (*panel B* of Fig. 4) only one did not show an increased excursion during PESP and the group as a whole also had significantly increased excursion 9.9 mm. ± 0.9 to 11.6 mm. ± 0.8, p < .001. Four in this subgroup did not have normal wall excursion at rest, but three reached the normal range with PESP. In the 11 patients with prior infarction *(panel C)*, three showed no increase in excursion with PESP but in the group as a whole, the change with PESP was again significant. 6.7 mm. ± 0.8 to 7.3 mm. ± 0.9, p < .05. Three patients had normal wall motion at rest. Eight patients in this subgroup did not have normal wall excursion at rest and six of the eight did not achieve normal excursion with PESP.

3. *Effect of PESP in relation to presence or absence of myocardial infarction.* Although PESP caused a significant increase in echocardiographic wall motion in all three subgroups plotted in *panels A, B and C* in Figs. 3 and 4, the increase in CAD regions with corresponding infarctions (i.e., *panel 3C combined with 4C*) was significantly less (by unpaired t test) than either the increase observed in regions without CAD *(panels 3A plus 4A)* or CAD regions without infarctions *(panels 3B plus 4B)*. These differences are graphically depicted in Fig. 5.

The effect of PESP in relation to prior infarction was also evaluated in the 24 regions plotted

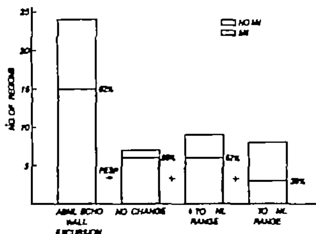


Fig. 6. Effect of postextrasystolic potentiation *(PESP)* in regions of abnormal *(ABNL)* echocardiographic *(ECHO)* wall excursion in relation to ECG evidence of myocardial infarction *(MI)*. Twenty-four regions had ABNL ECHO wall excursion. Fifteen of these regions had ECG evidence of MI. With PESP seven regions showed no change, and six of seven had MI, 9 regions improved, but to less than the normal *(NL)* range and six out of nine had MI. Eight regions improved to the normal range and only three out of eight had MI.

in Figs. 3 and 4 that showed abnormal wall excursion in the control state (Fig. 6). In 15 of these 24 regions, there was evidence of an infarction on ECG. During PESP seven regions showed no change and six of these had prior infarctions, and nine regions showed less than normal response with six of the nine demonstrating prior infarction. By contrast, of the eight regions that improved to the normal range with PESP only three had ECG evidence of a prior infarction.

4. *Relation Between Echocardiographic and Ventriculographic Findings.* In the 15 patients with biplane studies, a total of 30 regions of interest were evaluated, there were 12 regions of < 20 per cent systolic shortening (five septal and seven posterolateral wall). Eleven of these 12 regions also showed < 4 mm. (septal) or < 9 mm. (posterolateral) excursion on the echocardiogram—the exception being a patient with normal echocardiographic posterior wall excursion. Of the remaining 18 regions of normal systolic motion on the ventriculogram, there were two patients who demonstrated abnormal septal wall excursion on the echocardiogram.

In the seven patients with biplane cine studies that included VPB's, there were six regions of either reduced septal systolic shortening and/or reduced posterolateral systolic shortening. During PESP two of these six abnormally moving

*Region indicates either septal wall or posterior wall.

regions on the ventriculogram reached the normal range (i.e., > 20 per cent) and the same two of six similarly affected areas on the echocardiograms also reached normal excursion.

Discussion

Several aspects of this study merit particular attention (1) frequency of echocardiographic wall motion abnormalities in CAD (2) experience with noninvasive interventions during echocardiography in ischemic heart disease, and (3) implications of the effect—or lack of effect—of PESP in patients with CAD

Abnormal wall motion on the echocardiogram Despite recognized limitations of M mode scanning in CAD prior studies by several groups[2-4] have demonstrated that lesions of the LAD are often associated with abnormal septal wall motion. The most commonly employed measurement to describe this abnormality is septal wall excursion, and the lower limit of normal has ranged from 3 mm.[2-4] to 5 mm. in these studies. The frequency of reduced septal wall excursion in patients with LAD disease has varied with two groups reporting a frequency of 46 per cent[4] and two other groups a frequency of 80 per cent.[2] In the present study—using 4 mm. excursion as the lower limit of normal—we found reduced septal wall excursion in 52 per cent of our patients with LAD disease. The reasons for the variations between studies done at different institutions are severalfold and include ability in individual patients to successfully scan and record from the apex where abnormalities are presumably more marked, as well as inhomogeneity in the patient population so that varying numbers of patients from different series have prior myocardial infarctions, LAD lesions proximal to the first septal branch, well functioning collaterals to the LAD etc. It was not the purpose of the present study to attempt to further clarify such differences, but rather to establish a resting baseline in our patients so that we could then evaluate the effects of PESP (Since Joffe and colleagues have suggested the value of using the ratio of posterior wall to septal wall excursion rather than absolute measurements alone in identifying patients with LAD lesions—particularly proximal to the first septal branch—we also calculated this ratio but, like others, found it to have no significant advantage over absolute measurements) Our frequency of reduced posterior wall excursion (60 per cent) in patients with RCA and/or LCF disease is in the range reported by others—37 per cent and 52 per cent[4]—but again blood supply to this area is varied and our data serve primarily to establish a baseline for evaluating the effects of PESP

The relation between echocardiographic and ventriculographic evidence of asynergy has generally been good even when the right anterior oblique projection is utilized. We also found good correlations in a limited number of patients with left anterior oblique ventriculograms. Even though this view is better suited to visualize the same wall regions that are detected on the echocardiogram, the echocardiogram appears to be more sensitive to a reduction in septal wall motion in certain patients.

Noninvasive interventions during echocardiography Although it is often difficult to obtain technically good echocardiograms in patients who are performing dynamic exercise, static (handgrip) stress has been successfully attempted and transient abnormalities of septal motion in patients with coronary artery disease have been demonstrated during this stress.[12] That the echocardiogram can be used to investigate the effects of various pharmacologic interventions in ischemic regions of the heart has been demonstrated by Kerber and colleagues[13] in an experimental canine preparation, but there had been no prior clinical studies using inotropic agents. Several groups[14] have studied the effect of nitrates on abnormal wall motion, however and reported a beneficial response in patients with asynergy The mechanism of action of the nitrates is different from that of PESP and although of obvious clinical importance does not directly determine the response of ischemic or infarcted zones of myocardium to inotropic stimulation. Both methods of intervention echocardiography appear to be safe and reliable in humans, although an additional piece of equipment (the external cardiac stimulator) is necessary for consistently inducing VPB's noninvasively

Effect of PESP in CAD Animal studies have demonstrated that of the commonly used inotropic stimuli, PESP appears to be the most powerful stimulus of contractile reserve in ischemic myocardium. The results of these experimental studies have been applied to clinical studies employing cine left ventriculography and the response to PESP has been useful in demonstrating contractile reserve in local regions

of abnormal wall motion as well as in over-all ventricular performance. Thus, a significant response to PESP suggests that (1) local regions of asynergic myocardium are not irreversibly damaged and will show enhanced motion after revascularization, and (2) short term prognosis with either medical or surgical therapy approaches that of patients with normal wall motion.[19, 34] Adapting this technique to noninvasive cardiac evaluation (especially echocardiography) is now possible with the external mechanical stimulator developed by Zoll and colleagues. This device (Fig. 1) can safely and reproducibly introduce VPB's into the cardiac cycle. In the present study the effect of PESP on ischemic as well as presumably infarcted myocardium has been investigated noninvasively (Fig. 2). PESP caused a significant increase in wall excursion in all three groups of patients (Figs. 3 and 4), but the degree of improvement was significantly less in patients with ECG evidence of a transmural myocardial infarction in the affected region (Fig. 5). Because the response to PESP is variable in individual patients, the results can also be analyzed in a different manner. Using the same criteria (normalization of reduced motion) employed in our ventriculographic study of the effect of PESP on hemiaxial shortening, we found that eight regions of reduced septal or posterior wall excursion increased to the normal range with PESP while 16 did not (Fig. 6). Of the seven regions that showed no change at all, six were in areas of prior infarction. By contrast, only three of the eight regions that improved to the normal range had ECG evidence of prior infarction. Prior ventriculographic-pathologic correlations have shown that areas unresponsive or minimally responsive to inotropic stimulation are usually totally scarred while more responsive regions contain mostly viable muscle with or without some fibrous tissue.[31] (Similar pathologic findings have been reported in patients studied with nitroglycerin.[32]) Responsive areas have usually returned to normal function following myocardial revascularization.[14]

In conclusion, the present study suggests that (1) the combination of abnormal echocardiographic wall excursion and ECG evidence of a transmural myocardial infarction usually—but not always—indicates a poor response to PESP, hence probable limited myocardial viability and potential for improvement with revascularization; (2) the finding of abnormal echocardiographic wall excursion *without* definite ECG evidence of a prior infarction usually—but not always—indicates a good response to PESP. It should be emphasized that part of the unpredictability of the response to PESP in individual patients may be due to the unreliability of the ECG in reflecting areas of infarction (especially nontransmural infarction) that are subsequently demonstrated pathologically. Thus, an apparently normal region of myocardium on the ECG may not respond fully to PESP. In addition to "false-negative" ECG's, the opposite situation may also occur: the presence of a transmural infarction on the ECG may still be associated with enough islands of viable myocardium to produce a dramatic response to PESP.

Because of the limitations of the resting echocardiogram, noninvasively induced PESP or other forms of intervention echocardiography (such as with nitrates) may be useful adjuncts to the noninvasive evaluation of patients with coronary artery disease. By demonstrating the presence or absence of contractile reserve in patients with echocardiographic evidence of either ischemic or apparently infarcted myocardium, these techniques can help to evaluate (within the limits described above) the viability of the region in question. Whether these areas will return to normal function following revascularization can only be determined from ongoing surgical follow-up studies, but the prior experience cited with contrast ventriculography suggests that this indeed may be the case.

Summary

To evaluate noninvasively induced postextrasystolic potentiation (PESP) of ischemic or apparently infarcted regions of myocardium, an external mechanical cardiac stimulator (developd by Zoll) was used to induce ventricular extrasystoles during M mode echocardiography in 29 patients with coronary artery disease and in four control subjects. Twenty five patients had > 75 per cent stenosis of the left anterior descending artery including 13 with ECG evidence of anteroseptal myocardial infarction. 21 patients had > 75 per cent stenosis of the right coronary and/or left circumflex arteries, including 11 with ECG evidence of inferior and/or posterior myocardial infarction. Twenty four regions with reduced wall excursion showed vary

ing effects of PESP· eight regions improved to the normal range, while 16 did not. Twelve of the latter had ECG evidence of prior infarction. Similarly regions of asynergy that did not respond at all to PESP were usually but not always, seen in patients with infarctions. Based on prior ventriculographic-histopathologic correlates, non-responding regions are probably totally scarred with irreversible contraction abnormalities, whereas regions with evidence of contractile reserve are potentially viable. Because the ECG and resting echocardiogram are not totally accurate predictors of contractile reserve, noninvasively induced PESP may be a useful adjunct technique in delineating local contractile reserve in patients with echocardiographic evidence of hypocontractile myocardium of uncertain viability

The authors wish to thank Paul M. Zoll, M.D., for his cooperation in these studies.

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External noninvasive cardiac assistance and nitrate administration for patients with unstable angina pectoris or acute coronary insufficiency

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Unstable angina pectoris (crescendo anginal pattern with angina at rest despite adequate therapy) demands aggressive management. It has been shown that invasive circulatory assistance provided by intraaortic balloon counterpulsation does relieve and/or reduce chest pain in patients with unstable angina pectoris; however the effect of invasive circulatory assistance is transient in that the chest pain often recurs when the circulatory assistance is discontinued. Recently it has been reported that noninvasive circulatory assistance provided by external counterpulsation produces significant subjective and objective improvement in some patients with severe angina pectoris. The purpose of the present study was to assess the influence of external, noninvasive counterpulsation, alone and in combination with a vasodilator on left ventricular volumes and ejection fractions in patients with unstable angina pectoris or acute coronary insufficiency

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Methods

Patient population. Patients admitted to the *Coronary Care Unit at Parkland Memorial* Hospital in Dallas, Texas, with the diagnosis of unstable angina pectoris (defined as a crescendo anginal pattern, but no enzymatic or electrocardiographic evidence of myocardial infarction) and those with acute coronary insufficiency (defined as a single episode of prolonged chest pain, but without subsequent electrocardiographic or enzymatic evidence of infarction) were studied. Thirteen patients, 10 males and three females, aged 39 to 62 years (mean age 55 years) of whom eight had unstable angina pectoris and five had acute coronary insufficiency comprised the patient population studied. Three of the five patients with acute coronary insufficiency sustained the ischemic episode 4 to 8 days after a documented inferior myocardial infarction but showed no electrocardiographic, enzymatic or ^{99m}technetium stannous pyrophosphate (^{99m}Tc PYP) scintigraphic evidence of extension of the infarction. All patients were New York Heart Functional Class II or III. Patients with severe peripheral vascular disease (defined as an absent or diminished dorsalis pedis or posterior tibial pulse) and those above 68 years of age were excluded from the study. Five patients underwent cardiac catheterization, which revealed significant triple vessel disease in four patients and single vessel disease in one. No patient had scintigraphic or angiographic evidence of severe left ventricular dysfunction

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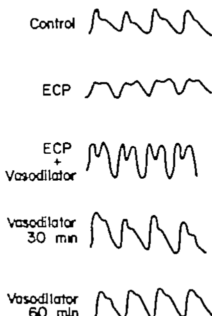


Fig. 1. Sample tracings of the arterial pulse obtained from finger plethysmograph during study. *ECP* = external counterpulsation, *ECP* + *vasodilator* = external counterpulsation combined with either isosorbide dinitrate or nitroglycerin. *Vasodilator* = responses 30 or 60 minutes after administration of isosorbide dinitrate or nitroglycerin.

(hypokinesis, akinesis, or dyskinesis) and no patient had clinical evidence of severe congestive heart failure, valvular heart disease, aortic regurgitation, diabetes mellitus, or pulmonary disease. Six patients had a history of hypertension but none of these were taking anti-hypertensive agents and each was normotensive at the time of the study. No patient was taking digitalis and all medications (i.e., propranolol, isosorbide dinitrate, nitroglycerin, etc.) were discontinued at least 8 hours prior to their study. Verbal and written informed consent was obtained from each patient prior to beginning the protocol.

Measurements. External counterpulsation was performed using a Cardiassist apparatus (Medical Innovations Inc., Waltham, Mass.). The patient's lower extremities were placed in the body suit device. External counterpulsation, synchronized with the QRS complex of the electrocardiogram and arterial pulse obtained from a finger plethysmograph, was applied in diastole to produce visual augmentation of the arterial diastolic pressure on the oscilloscope (Fig. 1). External counterpulsation pressures applied to the patients lower extremities ranged from 1.0 to .0 mm. Hg depending on patient comfort and the peak early diastolic pressure obtained.

The patient's heart rate and blood pressure were measured during each intervention. Because this study was totally noninvasive and due to the inability to precisely calibrate the arterial pressure obtained from a finger plethysmograph, the patient's blood pressure was taken by auscultation. Although blood pressure obtained by auscultation would not reflect augmentation of the arterial diastolic pressure produced by external counterpulsation, adequate early diastolic augmentation equal to or greater than the systolic pressure was ensured by visual display of the arterial wave form obtained from the finger plethysmograph (Fig. 1). Stroke volume was calculated by subtracting the scintigraphic end-systolic from end-diastolic volume.

The computation of ventricular volumes and ejection fractions was made utilizing a gated radionuclide blood pool scintigraphic technique. Electrocardiographically gated blood pool images were obtained in the 30 degree right anterior oblique (RAO) view as previously described in detail.[4] Blood pool labeling was accomplished by a modification of a technique previously described by us for *in vivo* labeling of red blood cells. A gating device (Physiological Synchronizer, Brattle Instrument Corporation, Cambridge, Mass.) was used to allow count acquisition in separate image frames during .05 sec. end systolic and end-diastolic periods. Approximately 250,000 counts were collected in each end-systolic and end-diastolic image. All scintigraphic data acquisition and processing were performed with the aid of a small computer (General Electric Med II). Left ventricular volumes and ejection fraction estimates were computed from the RAO images using the Sandler and Dodge length area method, as described in detail by Berman and associates[4] and by Salel and colleagues (Fig. 2).

Preliminary studies were conducted in 17 additional patients undergoing cardiac catheterization for a variety of reasons, including coronary artery disease, to be certain that our scintigraphic measurements of left ventricular ejection fraction correlated with the same information obtained angiographically. These patients were studied scintigraphically 1 to 25 days after or before cardiac catheterization (mean, 7.4 days). None of them demonstrated any important clinical change during the time that elapsed between the two procedures.

P otocol. On • the diagnosis of unstable angina

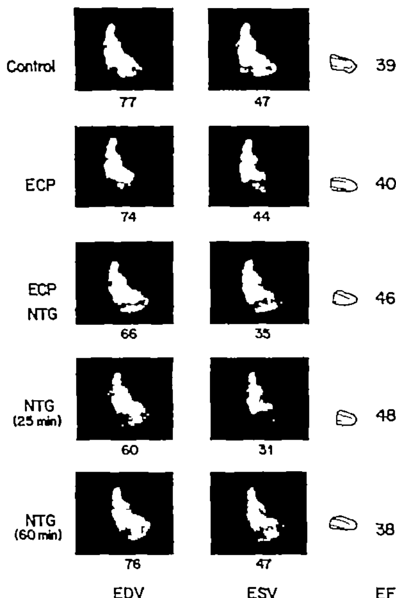


Fig. 2. Sample scintigraphic blood pool images with left ventricular end-diastolic volume *(left column)* and end-systolic volume *(middle column)* images taken from the right anterior oblique view. *ECP* = external counterpulsation, *ECP + NTG* = external counterpulsation combined with nitroglycerin, *NTG* = response 25 or 60 minutes after administration of nitroglycerin. The traced endocardial perimeters obtained from the respective images are shown in the *right hand column* and the ejection fraction indicated, end-diastolic perimeter = *solid line*, and end-systolic perimeter = *broken line*.

pectoris or acute coronary insufficiency (no enzymatic, electrocardiographic or ^{99m}Tc PYP scintigraphic evidence of myocardial infarction or recent extension of a previous myocardial infarction) had been made in patients admitted to the coronary care unit, they were selected into the present study. The patients were studied 4 to 18 days after hospital admission. If no ^{99m}Tc PYP myocardial scintigram had been obtained within 24 hours of this evaluation, the patient was injected with a 5 mg. bolus of stannous pyrophosphate (PYP) 20 minutes prior to the start of the study. This was done to allow the tin remaining in the blood following the PYP or ^{99m}Tc PYP injection to reduce ^{99m}Tc pertechnetate ($^{99m}TcO_4^-$) causing labeling of the red blood cells and thus creating the radionuclide blood pool necessary for the gated images. ^{99m}Technetium pertechnetate (15 mCi) was then injected into a peripheral arm vein and 30 minutes later myocardial imaging was

Table I

	HR (beats/min.)	*SV (ml.) (estimated)†*	*EDV (ml.)*	*ESV (ml.)*	*EF (%)*
Control	66 ± 5‡	75 ± 12	125 ± 18	49 ± 8	61 ± 2
ECP	69 ± 5	71 ± 17	114 ± 23	43 ± 6	60 ± 4
ECP + ISDN	71 ± 5	59 ± 8	100 ± 13*	42 ±	59 ± 4
ISDN (30 min.)	71 ± 6	53 ± 9*	93 ± 16*	40 ± 8	58 ± 2
ISDN (65 min.)	69 ± 6	57 ± 8*	96 ± 15	38 ± 7*	61 ± 2

HR = heart rate; SV† = stroke volume (EDV ESV); EDV = left ventricular end-diastolic volume; ESV = left ventricular end-systolic volume; EF = ejection fraction (EDV ESV) × 100/(EDV); ECP = external counterpulsation; ECP + ISDN = external counterpulsation combined with sublingual isosorbide dinitrate; ISDN = isosorbide dinitrate, administered 30 or 65 minutes prior to measurement.
*P < .05 compared to control.
‡SEM.

Table II

	HR (beats/min.)	*SV (ml.) (estimated)†*	*EDV (ml.)*	*ESV (ml.)*	*EF (%)*
Control	88 ± 4‡	52 ± 17	105 ± 30	54 ± 3	47 ± 3
ECP	90 ± 3	65 ± 23	112 ± 30	46 ± 9	56 ± 8
ECP + NTG	93 ± 1	4_ ± 9	82 ± 13	40 ± 4	50 ± 3
NTG (25 min.)	81 ± 10	44 ± 10	81 ± 13*	37 ± 10*	53 ± 3
NTG (60 min.)	83 ± 5	50 ~ 11	103 ± 14	53 ± 3	47 ± 4

HR heart rate; SV stroke volume (EDV-ESV); EDV = left ventricular end-diastolic volume; ESV left ventricular end-systolic volume; EF ejection fraction (EDV ESV) 100/(EDV); ECP = external counterpulsation; ECP NTG external counterpulsation combined with sublingual nitroglycerin; NTG nitroglycerin administered 25 or 60 minutes prior to measurement.
*P < .05 compared to control.
‡SEM.

begun in order to measure left ventricular volumes and ejection fraction. In addition, the control measurement set consisted of blood pressure and heart rate determinations.

External, noninvasive counterpulsation was then begun and 20 minutes later the measurement set was repeated. The counterpulsation was then discontinued for 15 minutes and subsequently reinstituted almost simultaneously with the administration of sublingual isosorbide dinitrate (10 mg.) in eight patients. The measurement set was again repeated 20 minutes later. The external circulatory assistance device was then discontinued and the measurement set repeated 10 and again 45 minutes later: these latter measurements were obtained 30 and 65 minutes after administration of isosorbide dinitrate, respectively.

Three patients were evaluated in a similar protocol as above, except sublingual nitroglycerin (0.4 mg.) was used instead of isosorbide dinitrate and the measurement sets were taken after 15 minutes of counterpulsation. In addition, two patients were studied using only external counterpulsation for 20 minutes with no vasodilator therapy.

The computation of ventricular volumes and ejection fractions were made utilizing the computer aided technique described above (Fig. 2). The measurement set taken at the completion of each experimental intervention was then compared to the control measurement set allowing each patient to serve as his own control. The differences in measurement sets were then compared using Student's t test for paired differences and considered statistically significant when $p < 0.05$.

Results

In the 17 additional patients in whom both scintigraphic and angiographic measurements of left ventricular ejection fractions were obtained there was a close correlation between the two different techniques for estimating left ventricular ejection fractions (r = 0.88). Thus, our scintigraphic approach for measuring left ventricular ejection fractions provides essentially the same information that one might obtain angiographically, thereby helping to validate the accuracy of the noninvasive scintigraphic measurements that we have made.

Left ventricular functional scintigraphic response to external counterpulsation. The effect of external counterpulsation on left ventricular volumes, ejection fractions, and other hemodynamic parameters is shown in Tables I and II. Although heart rate increased 10 ± 4 per cent (S.E.) (6 ± beats/minute, $p < 0.02$) with 20 minutes of external counterpulsation, blood pressure, and estimated stroke volume were not significantly altered. Twenty minutes of counterpulsation did not significantly alter left ventricular end-diastolic volumes (Fig. 3), end-systolic volumes (Fig. 4) or ejection fractions (Fig. 5).

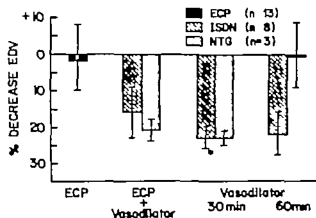


Fig. 3. Alterations in left ventricular end-diastolic volumes (*EDV*). Responses are expressed as per cent decrease ± SEM from control volumes. *ECP* = external counterpulsation, *ECP + vasodilator* = external counterpulsation combined with either isosorbide dinitrate or nitroglycerin. *Vasodilator* = *response 30 or 60 minutes after administration of* isosorbide dinitrate or nitroglycerin. ( ) = p < .05 with respect to control. Note the more prolonged effect of isosorbide dinitrate treatment.

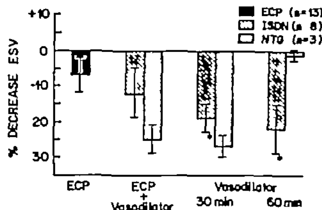


Fig. 4. Alterations in left ventricular end-systolic volumes (*ESV*). Responses are expressed as percent decrease ± SEM from control volumes. *ECP* = external counterpulsation, *ECP + vasodilator* = external counterpulsation combined with either isosorbide dinitrate or nitroglycerin. Vasodilator = response 30 or 60 minutes after administration of isosorbide dinitrate or nitroglycerin. ( ) = p < .05 with respect to control. Note the greater magnitude but shorter duration of response with nitroglycerin treatment.

Left ventricular functional response to external counterpulsation and vasodilator. The results of external counterpulsation combined with vasodilator therapy on left ventricular volumes, and ejection fractions and other hemodynamic parameters is shown in Tables I and II.

When isosorbide dinitrate (10 mg.) was combined with external counterpulsation blood pressure, heart rate, and estimated stroke volume were unchanged. End-diastolic volumes (Fig. 3) decreased 16 ± 7 per cent (p = 0.05). End-systolic volumes (Fig. 4) and left ventricular ejection fractions (Fig. 5) did not change significantly with the combined treatment.

When nitroglycerin (0.4 mg.) was combined with external counterpulsation, heart rate and *estimated stroke volume were unchanged. Blood* pressure obtained by auscultation showed that systolic blood pressure decreased 17 ± 3 per cent (p < 0.02) while diastolic blood pressure decreased 10 ± 2 per cent (p < 0.025). Scintigraphic left ventricular end-diastolic volumes (Fig. 3) decreased 21 ± 3 per cent (p < 0.01) and end systolic volumes (Fig. 4) decreased 25 ± 4 per cent (p < 0.02). Left ventricular ejection fractions (Fig. 5) were not significantly changed when nitroglycerin was combined with 15 minutes of external counterpulsation.

Left ventricular functional response to vasodilator. The results of the effect of vasodilator

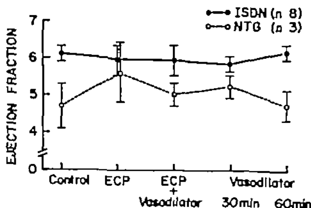


Fig. 5. Influence of various interventions on LV ejection fraction. Studies utilizing isosorbide dinitrate are represented by *closed circles—solid lines*, while those using nitroglycerin are represented *by open circles—dashed lines*. ECP = external counterpulsation, *ECP + vasodilator* = external counterpulsation combined with either isosorbide dinitrate or nitroglycerin. *Vasodilator* = response 30 or 60 minutes after administration of isosorbide dinitrate or nitroglycerin. Note that no intervention significantly altered ejection fraction.

therapy on left ventricular volumes, ejection fractions, and other hemodynamic parameters are shown in Tables I and II.

When the various parameters were measured 30 and 65 minutes after isosorbide dinitrate (10 mg.) administration, 10 and 45 minutes respectively after cessation of counterpulsation, heart rate and blood pressure were unchanged. Estimated left ventricular stroke volume decreased 22 ± 8 per cent (p < 0.025) and 23 ± 5 per cent

($p < 0.005$) at 30 and 65 minutes after isosorbide dinitrate administration respectively Left ventricular end-diastolic volumes (Fig. 3) decreased 23 ± 3 per cent ($p < 0.001$) and 22 ± 6 per cent ($p < 0.01$) at 30 and 65 minutes, respectively while end systolic volume (Fig. 4) decreased 19 ± 4 per cent ($p < 0.005$) and 22 ± 7 per cent ($p < 0.02$) at 30 and 65 minutes after isosorbide dinitrate administration respectively As in the other studies, left ventricular ejection fractions (Fig. 5) were not significantly altered

When the various parameters were measured 25 and 60 minutes after nitroglycerin (0 4 mg.) administration, 10 and 45 minutes after cessation of counterpulsation, respectively blood pressure heart rate and estimated stroke volume were unchanged. Nitroglycerin decreased left ventricular end-diastolic volumes 23 ± 2 per cent ($p < 0.005$) (Fig. 3) and end-systolic volumes 27 ± 3 per cent ($p < 0.005$) (Fig. 4) 25 minutes after its administration No significant changes in end-diastolic or end-systolic volumes were present 60 minutes after the administration of nitroglycerin. Left ventricular ejection fractions were unchanged by nitroglycerin (Fig. 5)

Discussion

External, noninvasive cardiac assistance has been used for many years. Dennis and associates were the first to employ a lower body sleeve in experimental animals. The technique has been extended to man with a device consisting of two large water filled sleeves placed about the legs and enclosed in an airtight seal. Available data from several previous studies have suggested that external counterpulsation effectively augments peak early arterial diastolic pressure and increases cardiac output but has little or no effect on preload The amount of diastolic augmentation is comparable to that produced by invasive intraaortic balloon counterpulsation but external counterpulsation lacks the additional effect of reducing afterload.

The diastolic augmentation has been shown by some groups to increase collateral coronary blood flow to ischemic myocardium The increased collateral coronary blood flow has been thought to be responsible for (1) improved metabolism in ischemic tissue (2) decreased mortality from coronary occlusion by embolism, (3) decreased epicardial ST segment elevation during experimental acute coronary occlusion, and (4) increased recovery of left ventricular function following ischemia.[27, 28] Other groups[27] have found that little or no change in coronary blood flow occurs with external counterpulsation. In addition Gowda and colleagues found that external counterpulsation did not alter the predicted creatine kinase infarct size in patients with acute myocardial infarction and in fact the size of the observed infarct was extended in several patients. The previous assessments of the influence of external counterpulsation on collateral coronary blood flow and protection of ischemic myocardium have therefore produced conflicting results.

The prospect that diastolic augmentation might increase collateral coronary blood flow with subsequent improvement of the pump action of the heart prompted this study In addition, studies in experimental animals have shown that intraaortic balloon counterpulsation combined with various pharmacological agents increases coronary blood flow greater than with either agent alone. It was hoped that external counterpulsation combined with vasodilator therapy would offer additional improvement in the pump action of the heart over external counterpulsation alone.

The results of the present study show that external counterpulsation did not significantly alter left ventricular volumes or ejection fractions. Similar results were found by Ryan and co-workers using angiographic techniques. External counterpulsation combined with vasodilator therapy was effective in reducing left ventricular end-systolic and end-diastolic volumes with nitroglycerin and end-diastolic volumes with isosorbide dinitrate but did not significantly alter left ventricular ejection fractions. The reduction of ventricular volumes theoretically would decrease energy requirements and increase the myocardial oxygen supply/demand ratio Although external counterpulsation combined with vasodilators reduced ventricular volumes, vasodilators alone were equally effective. Therefore it appears that combined treatment with external counterpulsation and vasodilator therapy offers no advantage over vasodilator therapy alone. Parmley and colleagues[11] used nitroprusside for systolic unloading combined with external counterpulsation f r diastolic augmentation and found that the predominant beneficial hemodynamic ffect of combined treatment were

produced by nitroprusside, thus supporting our present findings. Although coronary blood flow was not measured in our study the potential mechanical result of increased coronary blood flow i.e., improved pump function of the heart, was not evident with external counterpulsation.

The use of external counterpulsation in the treatment of severe angina pectoris has been suggested by several investigators previously who found significant subjective and objective improvement after external counterpulsation.[illegible] Solignac and associates[illegible] were unable to confirm these results, finding no significant improvement in hemodynamics or exercise angina threshold. In addition, Johnson and co-workers[illegible] found no dramatic improvement in anginal symptoms in patients after external counterpulsation treatment.

The beneficial effects of vasodilator therapy on ventricular volumes have been reported by numerous workers.[illegible] Clinical studies have shown vasodilators to be capable of reversing asynergic areas of ischemic myocardium[illegible] which might also be benefited by a coronary bypass graft. Patients whose hearts had asynergic regions unresponsive to nitroglycerin responded poorly to surgery Similarly those patients with ischemic heart disease but without evidence of previous infarction, showed greater improvement in pump response of the heart to nitroglycerin than those with evidence of previous myocardial infarction.[illegible]

It is evident from our data that nitroglycerin has a faster onset of action and a greater magnitude of response than isosorbide dinitrate, but isosorbide dinitrate has a more prolonged effect on ventricular volumes. The duration of action of nitroglycerin appears to be between 25 and 60 minutes, whereas isosorbide dinitrate is effective at least 65 minutes after its administration.

In summary the results suggest the following: (1) relatively short periods of exposure to external, noninvasive cardiac assistance do not alter left ventricular volumes or ejection fractions in patients with unstable angina pectoris or acute coronary insufficiency (2) external, noninvasive cardiac assistance combined with either isosorbide dinitrate or nitroglycerin offers no advantage over vasodilator alone in its effect on left ventricular volumes and ejection fractions in patients with acute ischemic heart disease and (3) isosorbide dinitrate and nitroglycerin therapy is effective in reducing left ventricular end-diastolic and end-systolic volumes in patients with unstable angina pectoris or acute coronary insufficiency for at least 25 minutes with sublingual nitroglycerin and 65 minutes for isosorbide dinitrate.

Summary

The influence of external, noninvasive counterpulsation alone and in combination with sublingual nitroglycerin or isosorbide dinitrate, on left ventricular volumes and ejection fractions was investigated. Patients with unstable angina pectoris or acute coronary insufficiency were selected for this evaluation. Left ventricular volumes and ejection fractions were estimated using a gated blood pool scintigraphic technique. Twenty minutes of external counterpulsation did not significantly alter left ventricular end-diastolic volumes, end-systolic volumes, or ejection fractions in 13 patients. When sublingual isosorbide dinitrate (10 mg.) was combined with 20 minutes of external counterpulsation in eight patients, left ventricular end-diastolic volumes decreased 16 ± 7 per cent ($p = .05$) but neither left ventricular end-systolic volumes (12 ± 7 per cent) nor ejection fractions were significantly changed. When sublingual nitroglycerin (0.4 mg.) was combined with 15 minutes of external counterpulsation in three patients, left ventricular end-diastolic volumes decreased 21 ± 3 per cent ($p < .01$) end-systolic volumes decreased 25 ± 4 per cent ($p < .02$) and ejection fractions were not significantly changed. When left ventricular volumes and ejection fractions were measured 30 and 65 minutes after isosorbide dinitrate administration, 10 and 45 minutes after cessation of external counterpulsation, respectively left ventricular end-diastolic volumes and end-systolic volumes were significantly decreased by approximately 20 per cent while ejection fractions were unchanged. When left ventricular volumes and ejection fractions were measured 25 minutes after nitroglycerin administration 10 minutes after cessation of external counterpulsation, end-systolic volumes decreased 23 ± 2 per cent ($p < .005$) and end-diastolic volumes decreased 27 ± 3 per cent ($p < .005$). No significant changes in left ventricular end-diastolic or end systolic volumes were seen 60 minutes after nitroglycerin administration. As in the other studies, left ventricular ejection fractions were unchanged. The results suggest that relatively short periods

of external, noninvasive cardiac assistance do not alter left ventricular volumes or ejection fractions in patients with unstable angina pectoris or acute coronary insufficiency. Although external counterpulsation combined with a vasodilator such as isosorbide dinitrate or nitroglycerin decreases left ventricular volumes, it offers no advantage over vasodilator treatment alone.

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Evaluation of phentolamine as a provocative test for idiopathic hypertrophic subaortic stenosis

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Idiopathic hypertrophic subaortic stenosis (IHSS) is characterized by a dynamic and variable obstruction of left ventricular outflow in contrast to the fixed obstruction of stenosis of the aortic valve.

The outflow obstruction in IHSS is caused by the severely hypertrophied interventricular septum in apposition to the anterior mitral leaflet. Subaortic obstruction is a dynamic process, the extent of which is determined from the intensity of left ventricular contraction, and changes in ventricular volume and in afterload[1-3] Many interventions decrease ventricular volume by decreasing venous return and thus reduce the stroke volume resulting in an increase of left ventricular outflow obstruction.

A decrease in venous return, such as that produced during the positive-pressure period of Valsalva's maneuver will result in an increase in the gradient across the left ventricular outflow tract. Drugs like amyl nitrite produces a fall in systemic arterial pressure and vascular resistance and an increase in heart rate cardiac index, and ejection velocity These changes in the circulatory state will increase the LV outflow obstruction. Maneuvers that increase ventricular contraction or that enhance emptying of the left ventricle are capable of increasing the subaortic obstruction.

Phentolamine, known to be an alpha adrenergic blocking agent also produces changes similar to beta adrenergic stimulation It results in hemodynamic changes including enhanced cardiac output by enhancement of ventricular contractility and slight increase in heart rate with a decrease in peripheral resistance. The increase in heart rate is usually minimal and probably represents a reflex baro-receptor response[4-6]

Because of these actions without notable induction of tachycardia and other side effects, phentolamine is potentially a better provocative agent than Valsalva's maneuvers, inhalation of amyl nitrate, or injection of isoproterenol to determine the extent of left ventricular outflow tract obstruction in the Cardiac Catheterization Laboratory and in particular in the Noninvasive Laboratory

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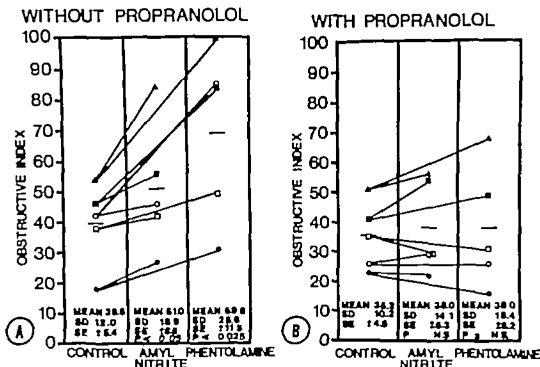


Fig. 1 A and B. *A*, Effect of amyl nitrite and 5 mg. of intravenously injected phentolamine on the echocardiographic OI before beta-adrenergic blockade. Changes of OI are assessed from paired t test. Horizontal lines in each column indicate the mean alues. *B*, Effects of amyl nitrite and phentolamine on the echocardiographic OI after beta-adrenergic blockade with propranolol. Significance of autonomic blockade on amyl nitrite and phentolamine testing is assessed from paired t test. Horizontal lines in each column indicat the mean values.

The purpose of this study is to evaluate (1) the relative effectiveness of phentolamine as com pared to amyl nitrite in determining the extent of obstruction of the aortic outflow tract in IHSS, (2) the effects of phentolamine on the obstructive index in patients with IHSS who have been treated with propranolol (3) compare the ease of use of phentolamine versus amyl nitrite as provocative tests in echo and phonocardiography

Methods

Equipment. A Smith-Kline Ekoline 20 ultrasoundscope with a 2.25 MHz 0.5-inch diameter transducer registered one-dimensional echograms. A Cambridge Multichannel amplifier and recorder were utilized to record and display the echo and phonocardiographic recordings. Recording was on photographic paper Cambridge-Leatham microphone recorded cardiac sound

Patient selection Idiopathic hypertrophic subaortic stenosis in all five patients was diagnosed on the basis of the following echocardiographic evidence. (1) abnormally thick ventricular septum with a ratio of septal wall to left ventricular free wall thickness 1.3, and (2) an abrupt systolic anterior motion of the anterior leaflet of the mitral valve (SAM) at a rate greater than that of the motion of the endocardium of the left ventricular posterior wall. No patient had other conditions that might alter septal thickness, such as hypertension, valvular cardiac disease right ventricular hypertension, or arteriosclerotic cardiac disease. The series included three men and two women whose ages ranged from 29 to 72 years, with an average age of 48.8 years. At the time of the first echocardiographic study none of the patients had been treated with propranolol.

A group of 35 patients with cardiac valvular pathologic conditions other than IHSS were included to determine the relative merits and safety of phentolamine versus amyl nitrite while recording echo and phonocardiograms.

Techniques. Each patient was supine and in basal condition when the first phonocardiographic and echocardiographic examinations were recorded. Recordings were made during and after several provocative maneuvers Valsalva's maneuver amyl nitrite, inhalation and phentol

Evaluation of phentolamine as a provocative test for idiopathic hypertrophic subaortic stenosis

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Idiopathic hypertrophic subaortic stenosis (IHSS) is characterized by a dynamic and variable obstruction of left ventricular outflow in contrast to the fixed obstruction of stenosis of the aortic valve.

The outflow obstruction in IHSS is caused by the severely hypertrophied interventricular septum in apposition to the anterior mitral leaflet. Subaortic obstruction is a dynamic process, the extent of which is determined from the intensity of left ventricular contraction, and changes in ventricular volume and in afterload. Many interventions decrease ventricular volume by decreasing venous return and thus reduce the stroke volume, resulting in an increase of left ventricular outflow obstruction.

A decrease in venous return, such as that produced during the positive-pressure period of Valsalva's maneuver, will result in an increase in the gradient across the left ventricular outflow tract. Drugs like amyl nitrite produces a fall in systemic arterial pressure and vascular resistance, and an increase in heart rate, cardiac index, and ejection velocity. These changes in the circulatory state will increase the LV outflow obstruction. Maneuvers that increase ventricular contraction or that enhance emptying of the left ventricle are capable of increasing the subaortic obstruction.

Phentolamine, known to be an alpha-adrenergic blocking agent, also produces changes similar to beta adrenergic stimulation. It results in hemodynamic changes including enhanced cardiac output by enhancement of ventricular contractility and slight increase in heart rate with a decrease in peripheral resistance. The increase in heart rate is usually minimal and probably represents a reflex baro-receptor response.

Because of these actions without notable induction of tachycardia and other side effects, phentolamine is potentially a better provocative agent than Valsalva's maneuvers, inhalation of amyl nitrate, or injection of isoproterenol to determine the extent of left ventricular outflow tract obstruction in the Cardiac Catheterization Laboratory and in particular in the Noninvasive Laboratory.

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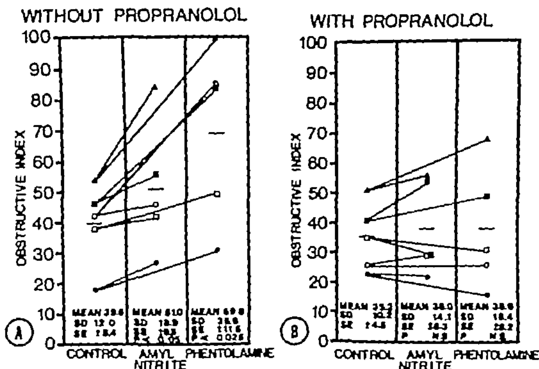


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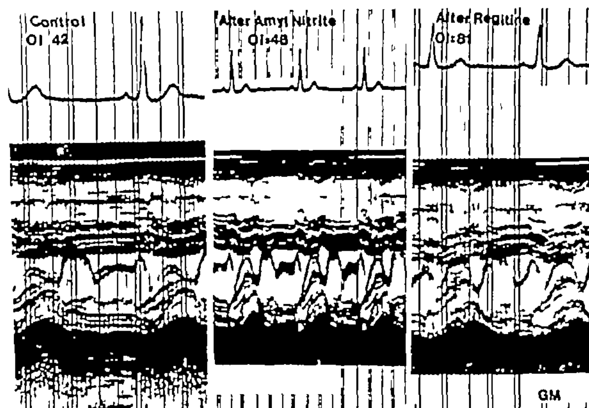


Fig. 2. Reproduction of part from continuous M-mode scan. The control obstruction index (OI) increased to 48 after amyl nitrite inhalation and to 81 after intravenous injection of phentolamine. The calculation of the OI was done at paper speed of 100 mm./sec. For illustration different paper speed was used.

amine 5 mg. bolus intravenous injection. The phentolamine test was performed only after the effects of inhalation of amyl nitrite had subsided completely which usually occurred within 10 to 15 minutes. After phentolamine was administered, the blood pressure was measured at intervals of 1 minute until the systolic pressure decreased at least 20 mm. Hg, at which time, the graphics were recorded.

After a 2 week course of oral ingestion of propranolol, 80 mg. daily the graphic (phonocardiographic and echocardiographic) examination with provocative maneuvers was repeated.

A. Echocardiographic examination. Each patient was studied in the supine position with the transducer in the fourth or fifth intercostal space along the left sternal border. The transducer was directed for simultaneous recording of the motions both of the anterior and of the posterior leaflets of the mitral valve, and then scanning was performed perpendicular to the left ventricular outflow tract until the maximal systolic motion of the anterior mitral valve leaflet was visualized. Ventricular systole was sub-divided into 30-millisecond segments, and an obstructive index (OI) was calculated by dividing the duration of narrowing by the average distance between the systolic septal thickness and the anterior mitral leaflet. The OI was calculated from the figure for the average of six consecutive beats at the point where maximum SAMing was obtained with the provocative maneuver. No correlation between the OI and the LV outflow tract gradient was done. The OI was used only for serial comparison. The recordings were done at a paper speed of 100 mm./sec. Septal thickness was measured below the level of distal margins of the mitral valve. The basal portion of the posterior left ventricle was measured by means of a T scan technique.

B. Phonocardiographic examination. During held mid-expiration phonocardiograms, carotid pulse tracings, and electrocardiograms were recorded simultaneously. With the patient supine the microphones were placed over the area where the systolic murmur was best heard. Sound signals were filtered into from 120 to 400 Hz and from 400 to 1 400 Hz bands. Recording

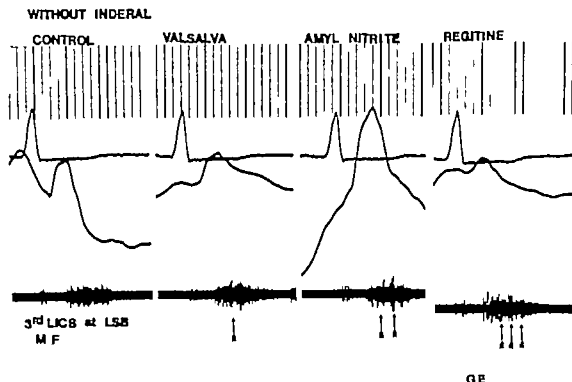


Fig. 3. Reproduction of phonocardiographic recording from the third left intercostal space *(LICS)* at the left sternal border *(LSB)* done in medium frequency range *(M F)*. The intensity of the systolic murmur is slightly increased by Valsalva's maneuver (↑)· moderately by amyl nitrite (↑↑), and severely by phentolamine (↑↑↑). The recording was done before beta-adrenergic blockade with propranolol.

speed was 100 mm./sec. All recordings in each patient were done from the same area and using the same baseline and sensitivity The changes induced by the maneuvers and drugs in the intensity of the systolic murmur were classified as. (1) slight, (2) moderate, and (3) severe accentuation of murmur

C. Catheterization. Right and left heart catheterizations were performed in 4 patients. The left ventricular outflow gradient was determined by double lumen Cournand 9-French catheter recording in the central aorta and left ventricle. The outflow tract gradient was recorded when the patient was in the supine basal state, and then after several provocative maneuvers in the following order· Valsalva maneuver at 30 mm. Hg, premature ventricular beats, inhalation of amyl nitrite, and injection of 5 mg. phentolamine. Simultaneous injection of contrast material into the right and left ventricles was performed to assess the thickness of the interventricular septum.

Statistical analysis was performed by the Student's t test for paired data.

Results

Results before induced blockade The control obstructive index (OI) prior to and following amyl nitrite and phentolamine are shown in Fig. 1A The mean value of the control OI is 39 ± 12.0. With inhalation of amyl nitrite the OI increased to 51.0 ± 18.9 ($P < 0.05$) and to 69.8 ± 25.6 ($P < 0.025$) after intravenous injection of phentolamine. Fig. 2 shows the changes in the OI obtained in one patient. The intensity of the systolic murmur increased slightly during Valsalva maneuver moderately after inhalation of nitrates, and markedly after injection of phentolamine (Fig. 3)

Table I summarizes the hemodynamic data obtained at catheterization and compares the basal state with amyl nitrite and phentolamine as a provocative test. Phentolamine elicited the largest increment in outflow tract gradient in all patients. Amyl nitrite inhalation induced the highest increment of the cardiac rate (mean 129 ± 7) while phentolamine elicited only a modest increase (mean 98 ± 7).

Results after induced blockade After two

Table I Catheterization data†

Patients	Control hemodynamics			Amyl nitrite			Phentolamine		
	HR	LV (mm. Hg)	Ao (mm. Hg)	HR	LV (mm. Hg)	Ao (mm. Hg)	HR	LV (mm. Hg)	Ao (mm. Hg)
1	75	—	—	120	—	—	96	—	—
2	80	144/10	134/65	125	160/10	110/60	110	160/10	90/60
		G = 10			G = 50			G = 70	
3	83	240/28	148/70	130	48/15	148/60	98	250/20	121/40
		G = 9			G = 100			G = 129	
4	63	185/10	143/65	132	185/18	125/60	96	196/14	123/60
		G = 42			G = 60			G = 75	
5	72	160/28	113/76	140	171/23	84/50	69	201/22	100/45
		G = 47			G = 87			G = 101	
	M = 75 ± 7	GM = 47 ± 34		M = 129 ± 7	GM = 4 ± 23		M = 93 ± 7	GM = 94 27	

HR = heart rate; LV = left ventricular pressure in mm. Hg; Ao = aortic pressure in mm. Hg; GM = mean left ventricular outflow gradient; M = mean heart rate.

= amyl nitrite versus control $P < 0.01$.

= phentolamine versus control $P < 0.01$ and versus amyl nitrite $P < 0.01$

†This table summarizes the hemodynamic data obtained by left heart catheterization of the left side of the heart in each of four patients, and compares the relative merits of Valsalva maneuvers, inhalation of amyl nitrite and intravenous injection 5 mg. of phentolamine. The amyl nitrite produced marked tachycardia when compared with phentolamine ($P < .02$).

weeks of beta-adrenergic blockade with propranolol there was no significant change from the baseline obstructive index (Fig. 4). In addition, amyl nitrite and phentolamine did not elicit any significant change of the control obstructive index (Fig. 1B). After amyl nitrite and phentolamine, the phonocardiogram did not record any appreciable change in the systolic murmur in the patients who had been given propranolol.

Phentolamine compared with amyl nitrite. In the 35 patients with mitral insufficiency who were given phentolamine 5 mg. intravenously there were no untoward side effects. High quality phonocardiograms and echocardiograms were recorded in all of the patients without difficulty.

The inhalation of amyl nitrite produced adverse reactions which included tachycardia, restlessness, headache, flush and dizziness, and thus made patient cooperation difficult. Ten phonocardiographic and 14 echocardiographic recordings were difficult to interpret. The average drop in blood pressure observed with phentolamine was 22 mm. Hg, with a maximum elicited heart rate of 92 ± 20. The amyl nitrite induced an average tachycardia of 132 ± 8. The poor recordings were in part related to the restlessness associated with headache and tachycardia.

Discussion

The diagnosis of idiopathic hypertrophic subaortic stenosis in a cardiac catheterization laboratory is based on demonstration of an outflow tract obstruction in the left ventricle that is dynamic and dependent on the size of the left ventricular outflow tract and left ventricular contractility. The outflow tract obstruction is enhanced by increased heart rate, nitroglycerin, amyl nitrite, post premature ventricular contraction, isoproterenol infusion, and isotonic exercises. The obstruction is relieved or lessened by decreasing heart rate, decreasing contractility with propranolol, increasing afterload in aortic outflow tract area by methoxamine, and increasing left ventricular outflow size by leg raising or intervascular volume expansion.

Diagnosis in the Noninvasive Laboratory is made by characteristic findings on echocardiography as well as phonocardiography with external pulse traces. Unfortunately, the provocative maneuvers utilizing the Cardiac Catheterization Laboratory are not as easily administered or performed on an outpatient basis. When characteristic echo and phonocardiographic findings are present the diagnosis of IHSS can be made with relative ease and assurance. On the other hand, many patients with precordial murmurs do not have classic findings and require some provocative maneuver to substantiate the diagnosis of aortic outflow tract obstruction. Similarly on echocardiography asymmetrical septal hypertrophy is frequently present without evidence of outflow tract obstruction and whether or not true

idiopathic hypertrophic subaortic stenosis is present requires provocation to elicit the outflow tract obstruction. Amyl nitrite and Valsalva maneuver have been classically utilized in the phono and echocardiographic laboratories. The Valsalva maneuver is easy to perform and frequently diagnosis can be made by auscultation of the increase in aortic outflow murmur with change in carotid pulse by palpation. The recording of the phonocardiogram and external pulse traces, however with Valsalva maneuver is difficult if not impossible on many patients because of artefact. Amyl nitrite is very effective in eliciting enhancement of the murmur of IHSS and conversion of the normal carotid to a typical percussion and tidal wave with delayed systolic expansion on apexcardiography as well. Like Valsalva maneuver however amyl nitrite not infrequently makes the recordings of the phonocardiogram as well as echocardiogram difficult to interpret because of tachycardia, patient restlessness or apprehension which all result in movement.

Phentolamine as demonstrated in our studies in the Cardiac Catheterization Laboratory produces an outflow tract obstruction at least equivalent to if not greater than amyl nitrite. In the Noninvasive Laboratory recordings after phentolamine were performed with ease and essentially without the patient's awareness of any symptoms.

Trials of ingestion of propranolol by patients with IHSS have been reported[13-] as producing symptomatic improvement in more than two-thirds of the patients. Hemodynamic studies[16] have shown minimal or no change of the left ventricular outflow tract in most of the patients with resting obstruction. However the propranolol prevented the increase of the gradient after exercise, thus giving an explanation for the clinical improvement. As in other studies, we found no significant change in the echocardiographic obstructive index in patients who were treated with propranolol for two weeks. However propranolol clearly prevented the enhancement of obstruction with provocative drugs such as amyl nitrite and phentolamine. This confirms the protective effect of propranolol on patients with dynamic outflow tract obstruction. On the other hand, it also suggests that patients who are on propranolol in whom the diagnosis is equivocal and requires provocative maneuvers should have the propranolol discontinued for 48 to 72 hours prior to the noninvasive or invasive testing, if provocative maneuvers are required to substantiate the diagnosis.

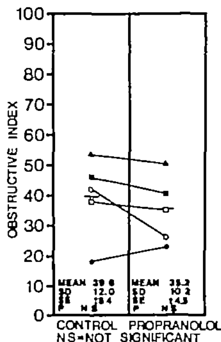


Fig. 4. After beta-adrenergic blockade with propranolol there is no significant difference between the control OI in the untreated and in the treated group. Horizontal lines in each column indicate the mean values. Significance of autonomic blockade on OI is assessed from paired t test.

In summary it appears as though phentolamine is more effective than amyl nitrite in eliciting aortic outflow tract obstruction in hypertrophic subaortic stenosis and can be utilized safely in the cardiac noninvasive laboratory to elicit obstruction and allow recording of high quality echocardiographic, phonocardiographic, and external pulse tracings.

Summary

Intravenous injection of phentolamine potentially offers a better provocative test for aortic left ventricular outflow tract obstruction than do Valsalva's maneuver, inhalation of isoproterenol, or of amyl nitrite. In hemodynamic studies, phentolamine enhanced myocardial contractility and decreased afterload with only induction of slight tachycardia. Phentolamine (5 mg.) was administered intravenously to five patients who had idiopathic hypertrophic subaortic stenosis, and 35 patients who had valvular dysfunctions, after which echocardiographic and phonocardiographic recordings were performed. Recordings were of

high quality despite changing hemodynamics. Systolic pressures fell an average of 20 mm Hg no pressure fell below 90 mm. Hg; there was no notable increase in heart rate. In the five patients with typical idiopathic hypertrophic subaortic stenosis, the amyl nitrite increased the obstructive index from 39.6 ± 12 to 51 ± 18.9 ($P < 0.05$) whereas, phentolamine increased the obstructive index to 69.8 ± 25.6 ($P < 0.015$). After a 2 week course of oral administration of 80 mg. of propranolol daily and then either inhalation of amyl nitrite or injection of phentolamine there was no change from the mean resting obstructive index. Phentolamine appears to be a safe, simple and specific diagnostic agent and more potent than amyl nitrite in eliciting dynamic obstruction in IHSS; phentolamine and amyl nitrite do not affect the obstructive index in patients with beta blockade.

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Phasic changes in human right coronary blood flow before and after repair of aortic insufficiency

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The following study was done to determine if there are changes in human phasic coronary blood flow before and after surgical repair of chronic aortic insufficiency and to determine if mean total coronary flow is altered by the low diastolic pressure which occurs with aortic insufficiency

Methods

Eight patients were studied at the time of open heart surgery for correction of severe aortic insufficiency Consent was obtained from each patient for the flow measurement at the time of surgery All patients had had a cardiac catheterization prior to surgery which demonstrated the following:

1 Moderate to severe aortic regurgitation with little or no aortic stenosis.

2. Angiographically normal coronary arteries with a dominant right coronary artery which supplied a significant portion of the left ventricle

3. All eight patients had good ventricular contractile function.

At the time of surgery prior to cannulating for cardiopulmonary bypass, the right coronary artery was exposed sufficiently near its origin to allow a Statham electromagnetic flowmeter probe to be placed on the vessel. Coronary blood flow ECG and the ulnar arterial blood pressure, which is routinely monitored, were recorded on a Hewlett Packard 4-channel recorder The electromagnetic flowprobes used in this study have been used repeatedly on over 200 saphenous vein bypass grafts where the accuracy of the electronic zero was checked by occluding the graft for 20 seconds.[1] The electronic zero was consistently within ±3 per cent. In addition the electronic zero was checked at the time of each right coronary artery flow measurement by placing the probe at rest in saline and comparing the mechanical zero with the electronic zero. We did not feel that it was justified to temporarily occlude the right coronary artery which is the best check on a reference zero.

After the aortic valve was replaced, 45 minutes after cardiopulmonary bypass was discontinued, and a normal heart rate and blood pressure were established, these measurements were repeated. It has been reported that coronary flow increases immediately after bypass and then gradually decreases for 20 to 30 minutes. We felt that 45 minutes after bypass the coronary flow should have stabilized. Mean right coronary blood flow was measured and that portion of coronary flow which occurred during systole and during diastole, respectively was determined by planimetry of ten consecutive cardiac cycles. The mean pressure through systole and also during diastole were measured by planimetry of the pressure curve for ten consecutive cardiac cycles. A pressure-rate product was determined for each patient before

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Table I Hemodynamic changes in eight patients with aortic insufficiency before and after valve replacement

	Aortic valve replaced		
	Before		*After*
Right coronary blood flow (mL/min.)	116 ± 37	$p < 0.005$	180 ± 40
Diastolic/systolic ratio	0.88 ± 0.17	$p < 0.005$	2.18 ± 0.8
Average mean arterial blood pressure (mm. Hg)	108 ± 17	NS	103 ± 13
Average mean systolic blood pressure (mm. Hg)	118 ± 10	NS	112 ± 11
Average mean diastolic pressure (mm. Hg)	67 ± 10	$p < 0.01$	66 ± 16
Heart rate (beats/min.)	84 ± 19	NS	90 ± 15
Average systolic resistance	1.106 ± 0.456	NS	1.293 ± 0.583
Average diastolic resistance	0.700 ± 0.240	$p < 0.01$	0.4 6 ± 0.219

artery has a lower diastolic to systolic blood flow ratio than branches of the left coronary artery. This is presumably since it supplies chiefly the right ventricle which does not produce sufficient systolic compression to interrupt flow. In all patients used in this study coronary angiography proved that the right coronary artery supplied a significant portion of the left ventricle. Also it was deemed important to study patients with good left ventricular function, since left ventricular failure has been shown to reduce the diastolic to systolic flow ratio.

Retrograde flow patterns during diastole have been observed in the femoral, brachial, and subclavian arteries in patients with aortic insufficiency. It is, therefore, not surprising to find significant decreases in diastolic coronary flow as well, with aortic insufficiency. We have previously shown in an animal model that short periods of acute aortic insufficiency produces a reversal of the coronary flow pattern with high flow during systole and low flow during diastole. At the end of two to three minute periods of acute aortic insufficiency in these animals there was always a period of hyperemia, suggesting that the adjustments in phasic coronary flow which occurred during acute aortic insufficiency were not sufficient to supply adequate coronary circulation. In addition there was a decrease in coronary sinus oxygen content suggesting that some myocardial ischemia was present during aortic insufficiency.

The results of this study of phasic coronary flow in man with chronic aortic insufficiency also suggest that total coronary flow is inadequate during aortic insufficiency since all eight patients showed a net increase in coronary flow after the aortic valve was repaired. It has been shown that the endocardium is relatively underperfused compared to the epicardium in dogs with aortic insufficiency using the microsphere method. It has also been shown that there is a decrease in total coronary flow with a redistribution of regional flow and an underperfusion of the endocardium, with acute arteriovenous fistula. It may be that in patients there is also a relative underperfusion of the endocardium during chronic aortic insufficiency because of the change from predominantly diastolic to predominantly systolic coronary flow. The increase in total coronary blood flow found in these subjects after valve replacement was a surprise to us. Neither the mean systolic pressure nor the mean heart rate changed significantly after valve repair and thus the calculated pressure-rate product does not suggest that a change in myocardial oxygen demand has occurred. Indeed the stroke volume and cardiac work are surely decreased by valve repair since aortic insufficiency was eliminated. The endocardium may have been relatively ischemic prior to valve repair due to the decreased component of diastolic flow which may have been due to the low diastolic pressure, associated with aortic insufficiency. Some subjects with acute and chronic aortic insufficiency have angina pectoris believed to be ischemic in origin, in spite of angiographically normal coronary arteries. This clinical decision can be difficult, but it is interesting that the three patients in this study with the greatest increase in coronary blood flow after valve repair were also the only three with chest pain which was thought to be angina.

In this study the coronary blood flow was actually measured in the large epicardial vessels. It is probable that with aortic insufficiency the low diastolic perfusion pressure leaves the epicardial vessels partially collapsed, and thus during systole with the large rise in pulse pressure the epicardial vessels can accommodate more blood before the effects of mural and extramural pressure become restrictive. A high systolic component of coronary flow was also recorded by Karp and Roe[8] in dogs with chronic aortic insufficiency. Also retrograde flow occurs in the femoral artery of human subjects with severe aortic insufficiency or a large patent ductus arteriosus, since apparently the resistance to forward flow through the femoral vascular bed is greater than the diastolic resistance to retrograde flow back into the aorta.

Reactive hyperemia was reported recently to be due to a "myogenic component" because of muscle relaxation in the vascular wall. If true this may occur chronically when there is aortic insufficiency and low diastolic pressure and it may take some time for the vascular tone, especially in the endocardium, to readjust when the aortic diastolic pressure rises after valve repair. Indeed it is conceivable that the vasomotor controls have been set at a low level for so long that the arteriolar muscle is not adequate to meet the elevated diastolic pressure after aortic valve replacement so hyperemia results. It is also possible that the short periods of ischemia which occur during the cardiopulmonary bypass release vasodilator substances which continue to cause vasodilatation after the cardiopulmonary bypass is discontinued, and thus may explain the increase in flow after valve repair. Perhaps the entire body response to cardiopulmonary bypass and cardiovascular surgery is instrumental in causing post-bypass coronary vasodilation in these subjects. By waiting 30 to 40 minutes after bypass, we hoped to minimize the changes in coronary flow occurring in the first 20 minutes after bypass.

Summary

We have shown previously that acute aortic insufficiency in chronically instrumented dogs reverses the normally high ratio of diastolic to systolic coronary blood flow.

Phasic blood flow in the dominant right coronary artery was measured directly with an electromagnetic flow meter during surgery in eight patients with severe aortic insufficiency before and after replacement of the aortic valve. Before the insufficiency was eliminated, right coronary flow averaged 116 ± 37 mL/minute and the diastolic to systolic flow ratio was 0.88 ± 17. Mean arterial blood pressure averaged 106 ± 17 mm. Hg, heart rate 84 ± 19 beats/minute and mean diastolic pressure averaged 67 ± 10 mm. Hg. After the aortic valve was replaced with an average heart rate of 90 ± 15 and mean blood pressure of 103 ± 13 mm. Hg, the average right coronary blood flow increased to 180 ± 40 mL/minute with a D/S ratio of 2.18 ± 0.8. In all cases the right coronary blood flow increased after the aortic insufficiency was eliminated surgically. Right coronary flow probably increased because of the improved diastolic perfusion pressure and the change from predominantly systolic to diastolic coronary flow.

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Gap phenomenon in the right and left bundle branch systems during retrograde conduction in man

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The phenomenon of gap in atrioventricular and ventriculoatrial conduction has been described in canine and human hearts.[1-4] As originally described by Moe and co-workers, the term gap in A-V conduction defines a time zone within the cardiac cycle during which premature atrial beats fail to propagate to the ventricles while atrial beats of greater and lesser prematurity elicit ventricular responses. Agha and associates described a similar gap phenomenon in bundle branches during antegrade conduction in man and classified it into three types (Types I, II, and III). It is the purpose of this report to describe two patients in whom gap phenomenon occured in bundle branches during retrograde conduction. Gap phenomenon in bundle branches during retrograde conduction is rare and was observed in only two of 60 patients who manifested reentry within the His-Purkinje system during ventricular refractory period studies. The observations made in these two patients may increase our understanding of impulse propagation in retrograde direction and the mechanisms of reentrant ventricular arrhythmias.

Methods

Right heart catheterization was performed in nonsedated postabsorptive state after obtaining an informed consent. Under local anesthesia a No. 7 tripolar electrode catheter was percutaneously introduced into the right femoral vein and positioned under fluoroscopic control in the region of the tricuspid valve for recording His bundle electrogram. A No. 6 quadripolar catheter was introduced into an antecubital vein and advanced to the high right atrium near its junction with the superior vena cava. The distal pair of electrodes was used to stimulate the atrium and the proximal pair to record a high right atrial electrogram. A No. 6 bipolar electrode catheter was percutaneously introduced into a separate antecubital vein and positioned under fluoroscopic control at the right ventricular apex for ventricular stimulation. Ventricular stimulation was performed using a programmed digital stimulator which delivered rectangular impulses of 1.5 msec. duration. A stimulus strength of twice diastolic threshold not exceeding 2 Ma. was used to stimulate the right ventricle. Intracardiac electrograms recorded at frequency setting of 40 to 500 Hz were displayed stimultaneously with the electrocardiographic Leads I, II, and V on a multichannel oscilloscope and recorded on paper.

Retrograde refractory periods were determined at more than one basic cycle length (V V) using the extrastimulus method. Following every eighth beat of the basic drive, a premature beat (V) was introduced at progressively decreasing (10 msec.) coupling intervals (V V) to the onset of ventricular refractoriness.

Definition of terms

S, V, H, A *represent the stimulus artifact,* ventricular electrogram, His bundle electrogram,

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and atrial electrogram of the basic drive beat.

S_2, V_2, H_2, A_2 represent the stimulus artifact, ventricular electrogram, His bundle electrogram and atrial electrogram of the premature beat.

Right bundle branch (RBB) system The conducting system between the site of stimulation (S) and the bundle of His (H) (S-H), when retrograde conduction of S impulse occurs via the RBB.

Left bundle branch (LBB) system The conducting system between the site of stimulation and the bundle of His (S-H), when retrograde conduction of S_2 impulse occurs via the LBB. The above definitions of bundle branch systems are arbitrary. Antegrade conduction intervals. See Ref. 10.

Retrograde conduction intervals. The stimulus artifact (S) was designated as the onset of induced ventricular depolarization and the S-H and S-A intervals were measured from the stimulus artifact to the onset of the His bundle electrograms and low atrial electrogram, respectively.

Retrograde refractory period measurements. The retrograde His deflections of impulses conducting in the retrograde direction for both the basic drive beats (V) and premature beats (V_2) introduced at long coupling (S S) intervals were hidden within their respective ventricular electrograms and could not be identified. Data from experimental studies indicate that at constant rates of stimulation the interval between the stimulus artifact and the retrograde His deflection is constant. During ventricular premature stimulation, retrograde conduction delay caused the H deflection to appear after the end of the ventricular electrogram. Thus H_2 deflection could be identified by its characteristic morphology expected time of appearance and physiologic behavior. The following definition of terms during retrograde refractory period studies apply to conduction through the normal pathways in the absence of functional bypass tracts.

Effective refractory period (ERP) of the His-Purkinje system (HPS) The longest V V interval at which the premature impulse blocks within the HPS. This can be determined only if the retrograde His bundle deflection of the premature beat is clearly identifiable prior to the blocked beats.

ERP of the right bundle branch (RBB) system The longest V V (S S) interval at which V blocks in the RBB and conducts retrogradely via the LBB with sudden prolongation of V_2H (S_2H) interval and results in a His Purkinje reentrant beat (V_3)[12]

ERP of the left bundle branch (LBB) system The longest V V (S_1S_2) interval at which V blocks in the infra His bundle region and is not followed by V_3. The ERP of LBB System can be determined only if V had been followed by V prior to the blocked beats.

ERP of ventricular myocardium Longest S_1S_2 interval at which S fails to evoke a ventricular response.

FRP of the ventricular myocardium The shortest V V interval in response to any S S intervals.

Case reports

Case 1 This was a 16-year-old asymptomatic woman with exercise induced ventricular tachycardia. Clinical evaluation revealed no evidence of heart disease. The resting ECG showed sinus bradycardia with intermittent junctional rhythm.

Electrophysiological studies revealed normal A H and H V intervals of 110 and 45 msec. respectively. During ventricular refractory period studies at a cycle length of 800 msec. (Fig. 1), the basic drive beats conduct to the atria. At a coupling (S S_2) interval of 370 msec. (Fig. 1 *panel A*) the S_2 impulse conducts retrogradely and the His-Purkinje (S H_2) and A V nodal (H_2A_2) conduction times measure 170 and 40 msec., respectively. At a shorter S S_2 interval of 360 msec. *(panel B)* S_2H interval increases to 215 msec. and H_2A_2 interval remains constant at 40 msec. A spontaneous ventricular beat (V) follows V and is preceded by an H V interval of 90 msec. (H V interval). The QRS morphology and axis orientation of V are similar to those in V_2, which suggests that the excitation during V also begins in the right ventricle. V is followed by another reentrant beat, V_4. Reentry (V) also occurred at a shorter S_1S_2 interval of 350 msec. When the S_1S_2 interval was further decreased to 340 msec. *(panel C)* V blocked in the infra His bundle region. At a shorter S_1S_2 interval of 330 msec. *(panel D)* V resumed conduction to the atria with an S_2H interval shorter than the S_2H interval in *panel B* (175 msec. vs. 215 msec.) and is not followed by V_3. The H_2A interval is constant at 40 msec. At a closer S_1S_2 interval of 320 msec. *(panel E)* V blocked again in the infra His bundle region.

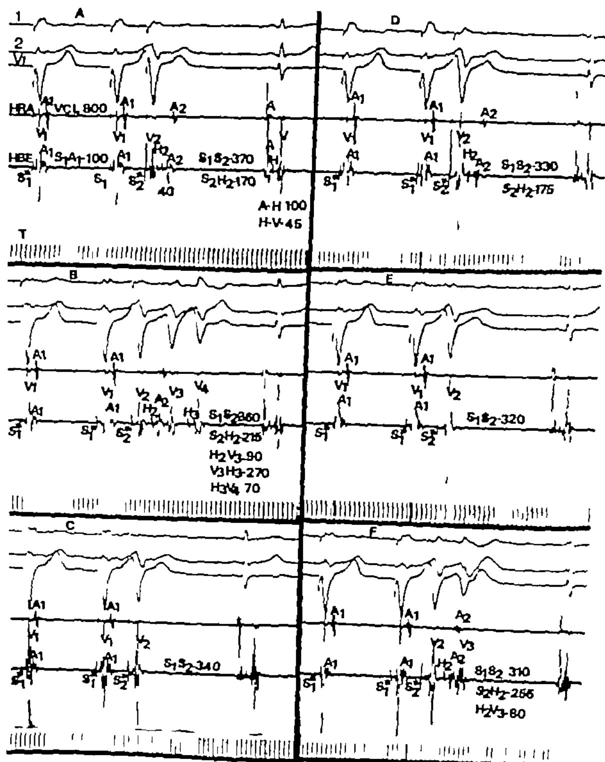


Fig. 1 (Patient No. 1) Gap phenomenon in bundle branches. During ventricular pacing there is 1:1 retrograde conduction. Note low to high sequence of atrial activation. In each panel standard ECG Leads I, II and V1 along with intracardiac electrogram from high right atrium (HRA) and His bundle (HBE) are recorded. Time lines (*T*) are 50 msec. apart. See text for details.

Retrograde conduction of S_2 impulse resumed at a shorter S_1S_2 interval of 310 msec. with an S_2H interval of 255 msec. which is longer than S_2H interval in *panel B* and results in a reentrant beat, V_r. Subsequent shortening of S_1S_2 interval produced reentry (V_r) to the onset of ERP of ventricular muscle.

Comment. In panel A because of lack of any significant delay in retrograde conduction through the His Purkinje System and the proximity of the stimulating site to the right bundle branch, the basic drive beats (V_1) and premature beat (V_2) reach the His bundle via the RBB. *In panel B* because of shorter coupling interval, the S_2 impulse blocked retrogradely in the right bundle branch (ERP of RBB) which is still refractory from the preceding basic drive beat, and propagates via the left bundle branch to the bundle of His (critical S_2H delay) and then returns antegradely via the RBB to reexcite the ventricular muscle which results in V_r. *In panel C* the S_2 impulse depolarizes ventricular muscle but blocks in both bundle branches (ERP of LBB and of HPS). *In panel D* the S_2 impulse resumed retrograde conduction via the RBB (gap in RBB). This is supported by an S_2H interval which is shorter than the critical S_2H interval and by the absence of V_r. The S_2 impulse blocked in both bundle branches in *panel E* and resumed conduction retrogradely via LBB (gap in LBB) in *panel F*. This is supported by an S_2H interval which is longer than the critical value and by the reappearance of V_r. *The duration of gap was 30 msec.* in both right and left bundle branch systems.

Fig. 2 (patient No. 1) illustrates the relationship of S_1S_2 and S_2H intervals to reentry and gap phenomena in bundle branches.

Case 2 This was a 52-year-old man with mitral valve prolapse and history of frequent palpitations. The resting ECG was normal.

Electrophysiological studies revealed normal conduction intervals during sinus rhythm. The A H and H V intervals measured 130 and 55 msec., respectively. Short runs of sinus node reentrant tachycardia were produced by premature atrial stimuli. Fig. 3, taken from a record of this patient, shows the gap phenomena similar to those in patient No. 1. The basic ventricular cycle length is 550 msec. in all panels. During ventricular drive there is no V A conduction. At an S_1S_2 interval of 370 msec. *(panel A)* the S_2 impulse

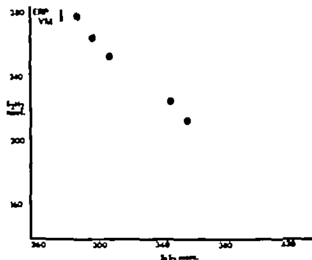


Fig. 2. (Patient No. 1). Gap phenomenon in bundle branches: The full range of S_1S_2 intervals *(abscissa)* are plotted against S_2H_2 intervals ( ) *(ordinate)*. Between S_1S_2 intervals of 410 to 370 msec. the S_2 impulse propagates retrogradely via the right bundle branch with increasing S_2H intervals. At an S_1S_2 interval of 360 msec. S_2 impulse blocked retrogradely in the right bundle branch (ERP of RBB) and conducted via the left bundle branch with critical S_2H_2 delay and caused reentrant beat, V (●). V phenomenon occured at shorter S_1S_2 intervals up to the point of effective refractory period of ventricular muscle *(ERP VM) except when S_2 impulse blocked in both* bundle branches (+ —S_1S_2 intervals of 340 and 320 msec.) or when S_2 impulse resumed conduction via the right bundle branch with S_2H_2 intervals shorter than the critical value (S_1S_2 interval of 330 msec.)

conducts with an S_2H_2 interval of 210 msec. and is followed by a sinus beat that blocks in the A V node. At a shorter S_1S_2 interval of 360 msec. *(panel B)* S_2 *conducts retrogradely* with a longer S_2H interval of 240 msec. (critical S_2H delay) and is followed by a His-Purkinje reentrant beat, V_r. The S_2 impulse blocks below the bundle of His at a coupling interval of 350 msec. *(panel C)* but resumes retrograde conduction to the bundle of His at a shorter S_1S_2 interval of 340 msec. *(panel D)* with an S_2H interval of 195 msec. which is shorter than the critical S_2H delay required for V_r to occur. Conduction of S_2 impulse to the bundle of His occured with shorter than critical S_2H_2 intervals up to an S_1S_2 interval of 310 msec. At these coupling intervals V_2 was not followed by V_r. The S_2 impulse blocked again below the bundle of His at an S_1S_2 interval of 300 msec. *(panel E)* and is followed by a sinus beat that blocked in the A V node (because it has not recovered from its depolarization by V_2). On further shortening the S_1S_2 interval to 290 msec.

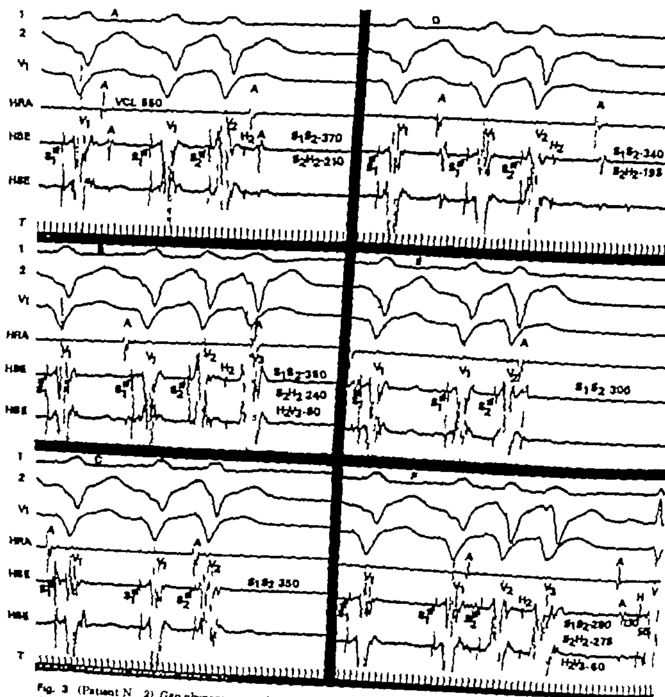


Fig. 3 (Patient N 2) *Gap phenomenon in bundle branches* During *entricular pacing atria and ventricles are dissociated* A sinus beat is show *Panel F* In each panel ECG Leads I, II and V nd intracardiac electrograms from the high right tri m (HRA) and His bundle (HBE) are recorded Time lines re 40 msec apart. See text for details

the S_2H_2 interval increases to 275 msec *which is* longer than the critical S H delay and is followed by V

Comment. In panel A V conducts retrogradely via the RBB *In panel B* the V impulse blocks in RBB and conducts retrogradely via the LBB *and* then conducts antegradely over the *RBB* reexcit ing the ventricle and resulting in V *In panel C* V resumes conduction retrogradely via the RBB (note shorter S H and absence of *V*) *V blocks* in both bundle branches in *panel E* (ERP of RBB or HPS) *In panel F* V conducts again retrogradely via the LBB and antegradely via the RBB and results in V *(Note longer S H interval) The* duration of gap in right and left bundle branches was 20 and 00 msec respectively

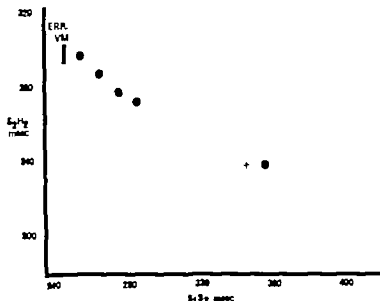


Fig. 4 (Patient No. 2). Gap phenomenon in bundle branches: The full range of S_1S_2 intervals (*abscissa*) are plotted against S_2H_2 intervals (•) (*ordinate*). Between S_1S_2 intervals of 390 to 370 msec. the S_2 impulse propagates retrogradely via the right bundle branch with increasing retrograde delays. V phenomenon (◉) first occurred at an S_1S_2 interval of 360 msec. when critical retrograde delay was ttained. Reentry continued t occur at shorter S_1S_2 intervals up to the point of ERP of ventricular muscle except when the S_2 impulse blocked in both bundle branches (+—S_1S_2 intervals of 350 and 300 msec.) or when S_2 impulse resumed conduction via the right bundle branch with S_2H_2 intervals shorter than the critical value (S_1S_2 intervals 340 to 310 msec.).

In Fig. 4 (patient No. 2) S_1S_2 intervals are plotted against S_2H_2 intervals. The His bundle deflection (H_2) of premature beat (S_2) emerged from ventricular electrogram at a coupling (S_1S_2) interval of 380 msec. At shorter S_1S_2 intervals the S_2 impulse conducts with longer S_2H_2 intervals and at an S_1S_2 interval of 360 msec. critical retrograde delay (critical S_2H_2) for intra His Purkinje reentry was achieved and S_2 is followed by a single reentrant beat, V (◉). The S_2 impulse blocked below the bundle of His at an S_1S_2 interval of 350 msec. and is not followed by His bundle deflection (+). Between S_1S_2 intervals of 340 to 310 msec. the S_2 impulse conducts with S_2H_2 intervals which are shorter than the critical delays required for V to occur. At a closer S_1S_2 interval of 300 msec. the S_2 impulse blocked again below the bundle of His and resumed conduction at still shorter S_1S_2 intervals with longer S_2H_2 delays and resulted in reentry (V) which continued up to the point of ventricular muscle refractoriness.

Discussion

The period of gap in antegrade bundle branch conduction describes a time zone during which premature atrial beats (A_2) at close coupling intervals conducted with complete bundle branch block pattern while premature atrial beats at earlier coupling intervals conducted with normal QRS pattern. Resumption of normal bundle branch conduction occurs because A_2 encounters delay in the A V node (Type I gap) or within the proximal His-Purkinje System (Type II gap) allowing time for the recovery of the previously refractory bundle branch. The mechanism of Type III gap in bundle branch conduction was less certain but the postulated hypotheses included true supernormal conduction and longitudinal dissociation.

During ventricular refractory period studies in our patients the manifested reentry within the His Purkinje System (V phenomenon), where the path of reentry incorporated both bundle branches and the bundle of His, allowed demonstration of gap phenomena in bundle branch systems during retrograde conduction. In this form of gap we assume that the V impulse initially blocked in the right bundle branch system and conducted retrogradely via the left bundle branch as manifested by critical prolongation of S_2H_2 interval and appearance of V_2.[11] At

closer coupling intervals, V which was blocked in LBB system resumed conduction via the RBB system with S_2H intervals shorter than critical value and was not followed by V. On further shortening the S S_2 intervals, however V blocked again in RBB system and resumed conduction via the LBB system with S H intervals longer than critical values and V reappeared.

During studies of antegrade conduction the refractory periods of bundle branches are identified by the appearance of typical bundle branch block QRS morphology. Such identification is not possible during retrograde conduction studies because QRS morphology during right ventricular stimulation remains unchanged. However the refractory periods of bundle branches during retrograde conduction can be determined in patients who manifest reentry within the His-Purkinje System. The occurence and determinants of this reentry have been previously described. In this form of reentry which occurs within a definable zone of S S_2 intervals, S impulse encounters retrograde block within the RBB system and propagates to the bundle of His via the LBB system. If propagation of S_2 to the bundle of His is sufficiently delayed (critical S_2H interval) right bundle branch will have adequate time for recovery to permit reexcitation of the ventricles by S impulse returning in the antegrade direction causing V_r. Once the critical S H delay is reached, V consistently occurred up to the onset of ventricular muscle refractoriness except when S encountered retrograde block in both bundle branches. However at closer S S intervals the S impulse resumed propagation to the bundle of His (H_2) (always with an S H interval exceeding critical S_2H) and reentry (V) was reestablished.

In both patients in this study the S H intervals of conducted beats following the initially blocked beats (*panels C and D* Figs. 1 and 3) were shorter than the critical delays required for V to occur. It is postulated that shorter S H intervals and consequently absence of V resulted from resumption of retrograde conduction of S impulse via the RBB system. Only after the premature beats blocked bilaterally again followed by resumption of conduction at still closer S S intervals with S_2H intervals longer than critical delays, did V phenomenon reappear (*panel E and F* Figs. 1 and 2). The reappearance of V coincident with longer S H_2 intervals indicate that S_2 impulse resumed conduction via the LBB.

The mechanism of these gaps is not clear but we believe is similar to the one proposed in Types I and II gaps in antegrade bundle branch conduction and involves proximal delay allowing distal recovery. Gaps in conduction are seen in a setting in which the ERP of a distal site is longer than the FRP of the proximal site so that at critical coupling intervals there is block at the distal site. Conduction is resumed at shorter S_1S_2 intervals because a sufficient conduction delay between the site of stimulation and the site of initial block permits recovery of the initially blocked distal site. The exact site of proximal delay is difficult to determine in the intact human heart. An increase of 5 to 15 msec. in the duration of latency was observed with early premature stimulation (Fig. 1 *panels D through F* Fig. 3, *panel F*) compared to late stimulation. This would suggest that a possible site of proximal delay was in the myocardium near the site of stimulation, but we did not find in other patients a relation between the duration of latency and the appearance of gap phenomenon. In most patients who did not demonstrate gap phenomenon the duration of latency increased in the same manner or even more with increasing prematurity. Data from experimental studies show that conduction delays and block can occur within the ventricular muscle at the muscle Purkinje junction, within bundle branches, and between the bundle branches and the bundle of His. The S_2H interval is a measurement of sum total of delays encountered by the S impulse within these multiple sites. Since the delays at each of these sites cannot be measured and direct recordings of the right and left bundle branches cannot be made in the intact human heart using the standard catheter recording techniques, it is not possible to define what portion of S_2H interval reflects the conduction time in the bundle branch systems. For similar reasons we cannot exclude the possibility of a true supernormal conduction as a mechanism for these gaps.[11, 13]

The similarities and differences between the gap phenomenon in bundle branches during antegrade and retrograde conduction are as follows.

1. The initial site of block in all types of antegrade bundle branch gaps is within some portion of the involved bundle branch. In retro-

grade bundle branch gaps the initial site of block is also within some portion of the involved bundle branch.

2. In antegrade gaps during periods of resumed bundle branch conduction the site of delay of A_2 is within the A V node (Type I gap) or within the proximal HPS (Type II gap). In retrograde gaps the site of proximal delay of S_2 impulse is between the point of stimulation and the recording site of bundle of His.

3. In antegrade gaps the localization of site of proximal delay is facilitated by the measurement of A_1A_2, H H and H V intervals in retrograde gaps the measurements are limited to S_1S_2 (V V) and S_2H (V_2H) intervals.

4. Typical bundle branch block patterns are seen on ECG in antegrade conduction QRS morphology remains unchanged during retrograde conduction. Furthermore, retrograde bundle branch gaps can be defined only in patients with manifest reentry within the His-Purkinje System.

Summary

Gap phenomenon in right and left bundle branch systems during retrograde conduction is described in two patients with manifest reentry within the His-Purkinje System (V phenomenon) In this form of gap the premature impulse (S_2) initially blocked in the right bundle branch system and conducted retrogradely via the left bundle branch system as manifested by sudden prolongation of S_2H interval and appearance of V_3. At close coupling intervals S_2 impulses encountered retrograde block in the left bundle branch system and resumed retrograde conduction via the right bundle branch system with S_2H_2 intervals shorter than critical value and was not followed by V_3. However on further shortening the S_1S_2 intervals S_2 impulse blocked again in right bundle branch system and resumed conduction via the left bundle branch system with S_2H intervals longer than critical values and V reappeared. The mechanism of these gaps is not clear but we believe is similar to the one proposed in Types I and II gaps in antegrade bundle branch conduction and involves proximal delay allowing distal recovery The similarities and differences between the gap phenomenon in bundle branches during antegrade and retrograde conduction are discussed.

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Case reports

Atropine-induced ventricular fibrillation: Case report and review of the literature

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Bradycardia occurs commonly during the early phases of acute myocardial infarction. Incidences of 25 per cent to 50 per cent have been reported in patients examined within the first hour subsequent to onset of symptoms. It has been suggested that bradycardia constitutes an important precursor of ventricular fibrillation and thereby contributes to early prehospital mortality from acute myocardial infarction. On the strength of this assumption atropine has been recommended in the routine therapy of early bradyarrhythmias, even when the latter are not associated with hypotension and ventricular ectopic activity. Moreover it has recently been advocated that during symptoms indicative of an impending myocardial infarction with concomitant bradycardia, high risk patients should be instructed to self-administer atropine by intramuscular injection.[4-6]

Recent observations, however, have raised serious doubts as to the advisability of this approach. Intravenous atropine, in the context of clinical and experimental myocardial infarction, has been shown to increase ischemic injury and decrease electrical stability of the myocardium.[10-14] The present report deals with a bradycardic patient with acute diaphragmatic myocardial infarction who developed ventricular tachycardia and ventricular fibrillation after intravenous administration of atropine. Previous case reports are reviewed and the electrophysiological mechanism and implications of this phenomenon are discussed.

Case report

A 63-year-old white male was admitted to the Intensive Coronary Care Unit at Rothschild University Hospital in Haifa, Israel, on June 20, 1977, with an acute diaphragmatic myocardial infarction. The diagnosis was documented by characteristic history, electrocardiogram, and enzyme changes. No signs of heart failure were present on admission nor were any noted throughout his stay in hospital. Past history was unremarkable. Initial tracings (Fig. 1A) performed 40 minutes after the onset of symptoms disclosed sinus bradycardia with rates between 45 and 55 per minute. Blood pressure was stable at 95/70 mm. Hg. In the 5 minutes following an intravenous injection of atropine sulfate 0.5 mg., a gradual acceleration of heart rate to 130 per minute took place followed by ventricular tachycardia (Fig. 1B), which degenerated into ventricular flutter (Fig. 1C) and ventricular fibrillation (Fig. 1D). The latter was promptly terminated by D.C. countershock. After reversion to sinus rhythm of 95 per minute, treatment with lignocaine was initiated with a 100 mg. intravenous bolus and a drip of 2 mg. per minute. Within two minutes, however, the heart rate again accelerated to 130 per minute with development of ventricular tachycardia and fibrillation again necessitating defibrillation. Establishment of sinus rhythm followed and the subsequent hospital course was uneventful except for a transient first degree atrioventricular block. Laboratory studies for electrolytes were all within normal limits.

Discussion

In the present case report, the following circumstances support a causal relationship between intravenous atropine and the ventricular dysrhythmia: (1) there were no previous ventricular ectopic beats prior to atropine administration; (2) the close temporal relationship whereby the atropine-induced cardio-acceleration was

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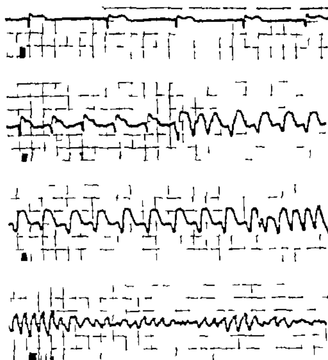


Fig. 1. Monitor leads taken sequentially. *A*, prior to intravenous administration of 0.5 mg. atropine showing irregular sinus bradycardia. *B*, Four minutes after atropine administration, sinus tachycardia of 130 per minute has ensued with development of ventricular tachycardia. *C*, Ventricular tachycardia degenerates into ventricular flutter and *D*, ventricular fibrillation.

seen to give rise to ventricular tachycardia and fibrillation within minutes of the intravenous injection.

The appearance of ventricular ectopy including ventricular tachycardia and ventricular fibrillation subsequent to atropine-induced rapid heart rates in patients with ischemic heart disease and acute myocardial infarction has been described.[14] Webb and associates, in a review of 74 patients examined within 30 minutes of the onset of acute myocardial infarction, reported a single case of ventricular tachycardia and fibrillation 3 minutes after intravenous injection of 0.6 mg. atropine. Morgensen and Orinius reported ventricular tachycardia and fibrillation which appeared "within minutes" of 0.5 mg. atropine. Massumi and colleagues[14] documented the appearance of ventricular tachycardia and fibrillation five minutes after 1 mg. atropine in a patient with ischemic heart disease and bradycardia. In a second myocardial infarction patient, short runs of ventricular tachycardia appeared four minutes after 1 mg. atropine. A third myocardial infarction patient developed a protracted sinus tachycardia of 130 per minute which degenerated into ventricular fibrillation after 20 minutes. Zipes and Knoebel[7] documented the appearance of ventricular tachycardia two minutes after 0.6 mg. atropine in one myocardial infarction patient and salvos of ventricular premature beats after 1 mg. atropine in another. Lunde reported ventricular tachycardia and fibrillation twelve minutes after 0.5 mg. atropine.

The purpose of the present communication is to highlight the potentially deleterious effect of atropine on the ischemic myocardium and to critically review the indications for its use in the bradycardic myocardial infarction patient.

Though the beneficial effect of atropine in the profoundly hypotensive and bradycardic acute myocardial infarction patient is well established, there have been recent suggestions as to the routine administration of atropine to mildly bradycardic patients who are otherwise entirely stable. This point of view was generated from the hypothesis that bradycardia per se is an important cause of electrical instability leading to ventricular fibrillation.[4-6] The high incidence (25 to 50 per cent) of bradycardia in the early phases of myocardial infarction coupled with the high incidence of early mortality due to ventricular fibrillation[10] suggested that immediate control of bradycardia might reduce mortality. The ready amenability of bradycardia to atropine administration naturally magnified the potential impact of this simple intervention on the natural history of myocardial infarction. As a measure to reduce the high prehospital mortality rate it has been recently advocated that high risk patients be instructed in the intramuscular self administration of atropine during symptoms indicative of impending myocardial infarction associated with bradycardia.[4-6] Recent evidence indicates, however, that the over all effect of atropine in this context may be unnecessary and potentially dangerous.

Clinical and experimental observations attest to the relatively benign nature of mild bradycardia and moderate hypotension in the course of acute myocardial infarction. Lower incidence of lethal ventricular dysrhythmia and lower hospital mortality rates have been recorded in bradycardic myocardial infarction patients as compared with those with tachycardia[11,12] and with those with normal heart rates. Patients with acute myocardial infarction and mild hypoten

sion without evidence of peripheral vasoconstriction were not found to have a significantly higher mortality rate than those without hypotension.[12] With regard to mild hypotension, it has been demonstrated that a sufficient increase in arterial pressure may be obtained in many cases by simply elevating the patient's legs.[13]

Potentially detrimental effects of atropine-induced rapid heart rates and lowered vagal tone have recently been reported. Knoebel et al. found that nutrient myocardial blood flow did not increase in patients with two and three atherosclerotic occlusive vessel involvement in response to atropine-induced cardio-acceleration. The authors conclude that in cases of severe ischaemic heart disease, rapid heart rates could thus potentially result in increased myocardial ischaemia. Such increased myocardial ischaemia following atropine-induced tachycardia manifesting as marked ST elevation has recently been demonstrated by Richman and is evident in one of the cases presented by Massumi and colleagues. It is pertinent in this context to note the recent demonstration by Jorgensen and associates[1] of a linear correlation in exercising humans between heart rate and myocardial oxygen consumption. The potential impact of these findings is reflected in a study by the Belfast mobile Coronary Care Unit, where, despite careful titration of the atropine dosage, inappropriately rapid heart rates were induced in 35 per cent of patients treated for bradycardia and hypotension. In an experimental model, increased heart rates during myocardial ischaemia were found to increase disparity of refractory periods in contiguous areas of myocardium, resulting in the establishment of multiple sites of reentrant activity fractionation of wave fronts, and eventually in ventricular fibrillation. In this same study the ventricular fibrillation threshold was found to be lowered by either increased heart rate, lowered vagal tone, or both as concomitantly induced by atropine.

The clinical relevance of these observations is dramatically demonstrated by the onset of lethal ventricular arrhythmia after atropine administration as evinced in the present case report. This albeit rare occurrence when considered in conjunction with the relatively benign prognosis of the mildly bradycardic but otherwise stable acute myocardial infarction patient, raises serious doubts as to the advisability of routine atropine administration in such cases. When associated with mild hypotension, the simple procedure of elevating the patient's legs may rectify the situation and obviate the administration of pharmalogical parasympatholytic agents. A more judicious use of morphine which further reduces heart rate[13] would, perhaps, reduce the prevalence and degree of bradycardia in this clinical context. A carefully considered approach is definitely warranted in light of the possibly superfluous and potentially hazardous effects of atropine.

Summary

A bradycardic and mildly hypotensive acute myocardial infarction patient developed sinus tachycardia, ventricular tachycardia, flutter and fibrillation following intravenous atropine. Previous case reports are reviewed and the literature regarding the advisability of this mode of therapy is discussed. In the light of conflicting opinion as to the necessity of atropine in the mildly hypotensive and bradycardic acute myocardial infarction patient and in view of its potentially deliterious effects on ischemic myocardium, a cautious and selective application of this drug is advised.

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Metastatic carcinoma presenting as obstruction to the right ventricular outflow tract

Report of a case and review of the literature

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Secondary involvement of the heart is relatively common at autopsy in patients with malignant disease,[1-9] but is seldom manifest, less frequently clinically significant, and only rarely the presenting feature.[10-13] The fifth reported case of metastatic carcinoma, in a 65-year-old male, causing significant outflow obstruction to the right ventricle, which in this instance was the presenting feature of an occult primary carcinoma of the colon, is discussed with a review of the literature.

Case report

A. T., a 65-year-old male, was admitted on October 24, 1976, to St. Paul's Hospital after having "collapsed" at home. He had experienced anorexia with a 15 pound weight loss over a year and more recently had ankle edema and increasing shortness of breath on exertion. He denied previous heart disease and took no medications.

On admission he was markedly weak, dyspneic, wasted, and complained of some chest pain. He was afebrile with a blood pressure of 120/70 mm. Hg and his cardiac rate was 104 per minute and regular. He had scattered petechiae over his body and gangrene of several toes and the tip of his nose with generalized peripheral cyanosis. His jugular veins were markedly distended with a liver enlarged 8 cm. below the right costal margin, soft and tender. Peripheral pulses were palpable and there was moderately severe ankle edema. His chest was clear to auscultation. There was a Grade 2/6 ejection systolic murmur at the second and third left intercostal spaces with a normal first and second heart sound. A fourth heart sound was heard.

Laboratory studies showed marked thrombocytopenia, hemoglobin of 9.1 gm. per cent and a leukocytosis of 22,000/mm. with a marked shift to the left. Prothrombin time was 27.5 sec. with a control of 12 seconds, partial thromboplastin time was 57 seconds with a control of 40 sec. The fibrindex was normal but with a weak clot, fibrin split products were greater than 10 mcg./mL and less than 40 mcg./mL. Blood gases showed a pH of 7.325, serum bicarbonate of 8.5 mEq./L. with a blood lactate level of 62.9 mg. per cent. The compensated lactoacidosis was thought to be due to decreased tissue perfusion from the shock syndrome in spite of the normal blood pressure. The patient was markedly oliguric due to decreased intravascular volume and probably poor cardiac output. The chest x-ray showed right atrial and right ventricular enlargement with sparse pulmonary vasculature and the ECG confirmed the radiological opinion of right atrial and right ventricular hypertrophy.

The working diagnosis at this time was severe pulmonary stenosis, although the normal second heart sound was disturbing. Recurrent pulmonary emboli with a recent large embolus was also seriously entertained.

Blood and urine cultures were drawn and the patient was given fresh frozen plasma, platelets, whole blood, and intravenous fluids. He, however, deteriorated clinically and decreasing vascularity of the lung fields was observed over a 3 day period. Therefore, right heart catheterization and pulmonary angiograms were to be carried out on an emergency basis on October 27, 1976, to establish a firm diagnosis and hopefully find a surgically correctible lesion.

A No. 6 Cournand catheter was passed through the right medial antecubital vein which showed a patent superior vena cava and no "V" waves in the right atrium. Right ventricular pressures were 60/16 to 18 mm. Hg. There was some difficulty experienced in passing the catheter through the pulmonary valve, but suddenly the pressure was markedly damped as the catheter advanced, and the catheter was quickly withdrawn 3 cm. back into the right ventricle. The patient rapidly lost consciousness and peripheral pulses became impalpable, in spite of sinus rhythm continuing, while the right ventricular pressures remained constant at 60/16 to 18 mm. Hg for the next 4 or 5 minutes.

Cardiopulmonary resuscitation was immediately initiated but was, however, ineffective from a cardiac output point of view and open chest massage was carried out with the thought that a right ventricular clot may have been pushed into the

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Fig. 1 Section of right ventricle through pulmonary valve *(top of photograph)* demonstrating impingement of tumor in the right ventricular outflow tract.



Fig. 2 Photomicrograph of infiltrative cecal carcinoma in the wall of the right ventricle.

outflow tract and the patient could be rapidly placed on open-heart bypass pump for embolectomy. This was unsuccessful, however, and the patient was pronounced dead 23 minutes after resuscitative procedures were started, 3 days after admission.

At autopsy [illegible] right ventricular intramural [illegible] carcinoma (Figs. 1 and 2) secondary from the [illegible] was found which compromised the outflow tract of the right ventricle just below the pulmonary valve, leaving lumen [illegible] slightly larger than the outside diameter of [illegible] There was no evidence of an atrial septal defect or [illegible] probe patent foramen ovale as possible cause for his arterial desaturation with reversed shunt due to the elevated right atrial pressure. Rectal and cecal neoplasms were present with metastases to liver, mesenteric fat, pancreas, and para-aortic lymph nodes.

Discussion

This patient presented in a moribund state primarily with signs of right ventricular failure and right ventricular outflow tract obstruction. He had nothing in his history that would have led one to believe that he had neoplastic disease except for his weight loss. Neoplastic disease was

considered on admission when he was found to have a picture consistent with microangiopathic hemolytic anemia, but no specific neoplasm could be found clinically.

Literature review

This case is of special interest in that it is one of the few reported instances of clinically significant intracavitary metastatic carcinoma to the outflow tract of the right ventricle. Moragues[10] reported a case of advanced malignant melanoma that showed a loud systolic murmur "at the mitral and pulmonic areas" which at autopsy had a large pedunculated tumor in the conus arteriosus almost plugging the pulmonic orifice. Blumenthal and Peterson reported a patient who at autopsy had an adenocarcinoma of the caecum with a secondary to the wall of the right ventricle completely filling the chamber and extending through the pulmonary valve with a history of dyspnea and a loud systolic murmur at the left of the sternum. McLoughlin reported a case of documented right ventricular outflow obstruction, probably secondary to bronchogenic carcinoma (no autopsy permitted) who had presented with congestive heart failure and weight loss. Most recently (1973), Gordon reported a case of metastatic renal cell carcinoma causing significant obstruction to the right ventricular outflow tract in a patient who had developed increasing right-sided congestive heart failure and a mid-systolic murmur at the pulmonic area. To our knowledge, this is then the fifth case of clinically significant intracavitary metastatic carcinoma to the outflow tract of the right ventricle. Our case is also of interest in that this patient with metastatic carcinoma to the heart presented as primary cardiac disease.

Secondary involvement of the heart is pathologically common at postmortem in patients with malignant disease being reported in from 3.4 per cent to 21 per cent in large series, [14, 14] and is almost invariably associated with widespread metastases[8] and rarely manifests itself as significant cardiac disease. The incidence has tended to increase in more recent series and will probably continue to do so because of an increased incidence of secondaries with prolongation of life in cancer patients due to modern treatment, an increased awareness of this entity and increasing longevity in the population.

Symptomatology from secondary neoplasm to the heart is, however uncommon. Although Burnett and Shimkin estimated 60 per cent of 53 cases of secondary involvement of the heart by neoplasm had signs or symptoms that might have indicated cardiac involvement, in their study were only two cases which had been diagnosed as having had cardiac involvement antemortem. Symptomatology could only be attributed to the cardiac involvement by secondary neoplasm in 13 per cent[8] and 8.5 per cent of patients in two large retrospective series.

Metastatic carcinoma presenting as cardiac disease in general would appear to be even less common. The series of Biran and colleagues of 723 consecutive autopsies that included 150 patients with malignant disease of whom 26 had secondary cardiac metastatic involvement, had two patients that presented with cardiac symptomatology as well as manifestations of their neoplastic process as the first sign of disease. Both cases manifested congestive heart failure and pericardial effusion as the presenting feature of carcinoma of the lung.

A review of the literature for the past ten years disclosed only two cases of occult carcinoma presenting clinically as primary cardiac disease. In one, Spinaldo-Franco and associates reported the case of metastatic ovarian squamous cell carcinoma to the left ventricle, and the other was mentioned above.

In summary then, this is the fifth reported case of metastatic carcinoma presenting as obstruction to the right ventricular outflow tract.

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Clinical pathologic conference

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Dr. James L. Anderson The patient was a four year-old girl with a 15 month illness. The family history was non-contributory She was asymptomatic with normal growth and development until the age of three years. At the onset of the illness, she had episodes of sudden abdominal pain, weakness, cough, and cold sweats lasting from 15 to 40 minutes and occurring nearly every morning. She was rational during these spells except on two occasions when the eyes rolled and she lost consciousness, but without convulsive movements or incontinence. These symptoms were worse when she assumed the recumbent position they were not related to activity and were usually followed by a refreshing sleep. She was apparently active and asymptomatic during the daytime following these events. After three months, she was hospitalized in a neighboring community with no abnormal cardiologic findings. A thoracic roentgenogram was reported as being normal. After neurological evaluation, including electroencephalography (EEG), phenobarbital and, later diphenylhydantoin were prescribed for a possible abdominal seizure disorder but without improvement.

These episodes became more prominent and continued to occur nearly every day She was readmitted to the hospital ten months later having had a weight loss of one pound in the interval. Vital signs included a cardiac rate of 88 beats per minute and a respiratory rate of 28 per minute. The blood pressure was 90/40 mm. Hg. The hepatic edge was 4.5 cm. below the right costal margin. The second cardiac sound was accentuated and single. There was no murmur A thoracic roentgenogram at this time revealed a prominent right ventricular outflow tract and increased perihilar markings. Another EEG now revealed sharp waves of a discharging focus in the left temporal area. Diagnoses of a carcinoid tumor and porphyria were considered. She was readmitted to the hospital for a third time two months later on October 23, 1975 because of the onset of pedal edema, increased tiredness, shortness of breath, and a weight gain of three pounds. There were signs of congestive cardiac failure with a gallop rhythm and hepatomegaly (lower edge 6 cm. below the right costal margin) The cardiac shadow had enlarged and an electrocardiogram (ECG) now revealed right ventricular hypertrophy She improved temporarily with digitalization and diuretic therapy but she became tachypneic again and was transferred to St. Marys Hospital Medical Center Madison, Wisc., one week later on October 30 1975.

Examination on admission revealed a severely distressed child with a carinate prominence of the thorax. Vital signs included a cardiac rate of 132 beats per minute and a respiratory rate of 64 per minute, and the blood pressure was 98/68 mm. Hg. The first cardiac sound was followed by a Grade II/VI systolic murmur at the lower left

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Fig. 1 Frontal view of thoracic roentgenogram.

sternal border an accentuated single second and a Grade III/VI decrescendo diastolic murmur transmitted along the left sternal border The hepatic edge projected 6 cm. below the right costal margin. The arterial pulses were of narrow contour and small volume, and cervical veins were distended.

At this time I will ask Dr Durnin to present the radiographic findings, to be followed by Dr Ledbetter who will present additional cardiac data and the differential diagnosis.

DR. ROBERT E DURNIN The portable film of the chest (Fig. 1) is compared with recent and outside films. The current radiograph, as well as recent films, reveals mild cardiac enlargement with pulmonary edema. No definite pleural effusions are seen The prominence of the pulmonary artery is abnormal and suggests pulmonary hypertension. The presence of pulmonary edema in this setting suggests post-capillary pulmonary hypertension or left atrial blockade

DR. MARION K LEDBETTER This child's severe symptoms, the most prominent of which was abdominal pain were periodic and not continuous through the day or night Signs of cardiac disease did not appear until relatively late in the course of the illness, although it was apparent during the hospital admission just prior to transfer to St. Marys Hospital Medical Center that she had a severe cardiovascular disorder The abdominal pain and EEG findings apparently had been misleading in suggesting a seizure disorder The pain may have been anginal in nature secondary to congestive cardiac failure and coronary insufficiency Swelling of the hepatic capsule may also be a painful event when venous pressure becomes severely elevated. Worsening of the paroxysms of cough, pain and diaphoresis in the recumbent position, as described by Dr Anderson, would suggest pulmonary venous congestion as commonly occurs in mitral stenosis.

In the differential diagnosis of cardiac disease, I would consider obstruction of pulmonary venous drainage with proximally elevated circulatory pressure. The ECG (Fig. 2) revealed a prominent degree of right ventricular hypertrophy with right axis deviation, prominent R waves in right precordial leads, and a small rS ratio in left precordial leads. These ECG findings suggested that the cardiac lesion was probably located at or proximal to the mitral valve. Lesions of such a nature may be separated into those of congenital origin and those acquired post natally The absence of symptoms before the age of three years tends to militate against a diagnosis of congenital cardiac disease, but not conclusively Pertinent congenital cardiac lesions include total anomalous connection of pulmonary veins, pulmonary venous stenosis or atresia, cor triatriatum, supravalvular stenosing ring of the left atrium, premature closure of the foramen ovale, and mitral stenosis. Acquired conditions which may cause pulmonary venous obstruction include granulomatous disease of the lungs, such as tuberculosis, and also constrictive pericarditis, left atrial myxoma, and pulmonary veno-occlusive disease. Primary pulmonary hypertension involves a pre-capillary obstructive disease process. This diagnosis was of prime consideration at the time of hospital admission.

We continued efforts to compensate the myocardium. On the day following admission to St. Marys Hospital, we proceeded with cardiac catheterization (Table I) This was done with the patient semirecumbent and while breathing oxygen through a mask. Cyanosis and distressed breathing persisted throughout the procedure. Aortic and venous oxygen saturations were severely depressed, and systemic venous pressures were elevated with prominent a waves (Fig. 3). The pulmonary arterial pressure was elevated

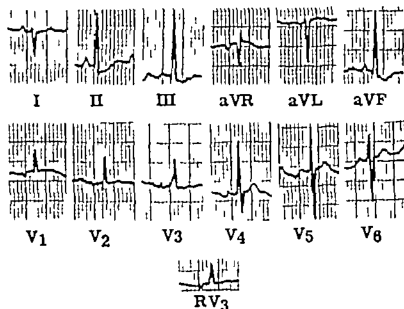


Fig. 2. Electrocardiogram.

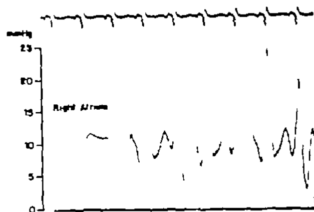


Fig. 3 Right atrial pressure.

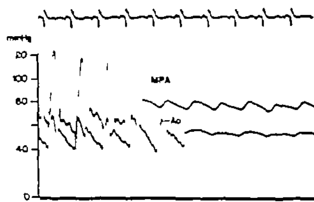


Fig. 4 Pulmonary arterial (*MPA*) and aortic (*Ao*) pressures.

above the aortic pressure (Fig. 4) A pulmonary arterial wedge pressure could not be obtained. Prolonged components of a cardiogreen dye curve indicated a slow circulation compatible with congestive cardiac failure. The cardiac index was 2.6 liters/min./M The pulmonary resistance was calculated to be 2.5 times that of the systemic resistance.

Dr Durnin will present the cineangiocardiograms and the right ventriculogram.

DR. DURNIN The left ventricular cineangiogram reveals a normal appearing and contracting left ventricle (Fig. 5). The mitral valve was not well evaluated. There is no evidence of (1) a left to-right shunt, (2) deformity of the left ventricular outflow tract, (3) an obstructive lesion, or (4) endocardial fibroelastosis. The aortic root appears normal and there was neither a patent ductus nor coarctation of the aorta. By the course of the right coronary artery one can assume that there is significant right ventricular hypertrophy Injection into the pulmonary artery shows dilatation of the main pulmonary artery and its primary branches. Some pulmonary regurgitation is noted, but this may be due to recoil of the catheter The pulmonary arteries appear very large and dilated centrally These vessels show a corkscrew appearance as they approach the mid lung field area. After this, these vessels taper very rapidly This radiographic finding is characteristic of a marked increase in pulmonary vascular resistance. Pulmonary blood flow is slow and the



Fig. 5. Left ventricular cineangiogram in left anterior oblique view

levophase is never appreciated from the standpoint of viewing the pulmonary veins or the left atrium From this injection alone cor triatriatum or left atrial blockade could not be excluded. Following injection into the right ventricle, biplane angiocardiograms revealed dilatation and hypertrophy of the right ventricle with slow forward movement of the contrast material. After the total duration of filming which was 7.5 seconds, the right ventricle (Fig. 6) remained opacified and the levophase of the pulmonary circulation was not observed. In summary the studies reveal a normal appearing left ventricle and there is no evidence of an obstruction or a left to-right shunt either at the ventricular or major arterial level. A slow circulation time was also demonstrated. The angiographic characteristics of the pulmonary angiogram would be consistent with severe pulmonary hypertension. The exact site of obstruction is not definitely defined.

DR. LEDBETTER My diagnosis is primary pulmonary hypertension, with a possibility that the child had pulmonary veno-occlusive disease. The data of cardiac catheterization in these two conditions are similar except that in primary pulmonary hypertension the pulmonary artery wedge pressure is normal, but it is only sometimes elevated in pulmonary veno-occlusive disease. Had her condition permitted a biopsy of the lung would have been indicated however she died on

Table I Cardiac catheterization data

Site	Pressure (mm. Hg)		O saturation (%)
	Systolic/diastolic	Mean	
Superior vena cava	24/6	15	25
Right atrium	25/17	—	21
Inferior vena cava	22/10	15	24
Right ventricle	122/0	—	21
Main pulmonary artery	124/55	77	24
Left ventricle	‾0/0	—	70
Aorta	‾0/39	54	68

the second day following hospital admission.

Dr Angevine will present the gross autopsy findings.

DR. JAMES M ANGEVINE. The autopsy showed pleural effusions of 150 ml. bilaterally The main abnormality of the heart was hypertrophy of the right ventricular wall, with moderate dilatation of the right ventricular chamber (Fig. 7). The thickness of the right ventricular wall ranged from 0.5 to 0.7 cm. The left ventricular chamber was normal, its wall measuring 1.0 cm. The pulmonary trunk was distended, with a diameter of 2.7 cm., while the diameter of the ascending aorta was 1 6 cm. Each of the valves, as well as the coronary arteries, were normal. The left atrial chamber was normal and received normal pulmonary veins. The ductus arteriosus was represented by a ligament. The ventricular septum was intact, as was the atrial septum the foramen ovale being anatomically sealed.

The lungs, after being removed, failed to collapse materially They were firm, and their cut surfaces were brown and exuded a small amount of frothy fluid The elastic arteries were distended Dissection of the pulmonary arteries showed tiny yellow intimal streaks in the distal vessels. The pleural lymphatics appeared unusually prominent.

Of the abdominal organs, the liver and spleen showed classic signs of chronic passive congestion. The brain was normal.

Dr Gilbert will review the histologic findings.

DR. ENID F GILBERT- Histologic examination of the lungs revealed a fairly uniform picture. There was tortuosity and widening of alveolar capillaries. The alveolar spaces contained precipitated edema fluid and macrophages. Some of the latter contained cytoplasmic hemosiderin. The



Fig. 6. Late phase of right ventriculogram showing continued opacification of the right ventricle. The catheter through which the contrast material had been injected into the right ventricle has retracted into the right atrium. The other catheters are in the apex of the right ventricle and in the ascending aorta.

interlobular septa were edematous and contained dilated lymphatics (Fig. 8*a*) The latter were in communication with dilated pleural lymphatics (Fig. 8*b*)

Prominent obstructive changes were present in the pulmonary venules and small veins. These were characterized by intimal fibrosis (Figs. 8*c* and *d*). In venules, this tissue tended to be avascular while in the small veins the fibrous tissue contained vascular spaces (Fig. 9*a*) In some veins, the fibrous tissue was deposited as mural plaques. In some small veins the muscular coat was distinct, giving a suggestion of the feature seen in arterial walls (Fig. 9*a*) The arterial system was characterized by medial hypertrophy of large and small muscular arteries without intimal change (Fig. 9*b*) The pulmonary trunk showed a thick media with retention of continuous elastic fibers, the pattern resembling that of the aortic media. In addition the media showed cystic medial necrosis characterized by the presence of numerous basophilic amorphous microcysts. These lay between elastic fibers but did not interrupt their continuity

The liver showed central hemorrhagic necrosis, while essentially normal features were observed





Fig. 7 and b. a, Right atrium and right ventricle. Hypertrophy and dilatation of right ventricle. Tricuspid valve is normal. b Right ventricle, pulmonary valve and pulmonary trunk. Dilatation and hypertrophy of right ventricle. Dilatation of pulmonary trunk. The pulmonary valve is normal.

in the myocardium, brain, and the other organs.

Our pathologic diagnosis of the primary condition is pulmonary veno-occlusive disease. I shall ask Dr Edwards to present a closing discussion.

Dr. Jesse E. Edwards The pathologic changes described by Drs. Angevine and Gilbert are classical for the condition named in 1966 by Heath and associates as pulmonary veno-occlusive disease. It is a rare condition. In 1976, Wagenvoort indicated that there were 31 reported cases in the literature. The condition is about equally distributed between males and females. It is usually observed in children and



Fig. 8 through d. Photomicrographs of pulmonary tissue. a, Edema of interlobular septum in which dilated lymphatics (*L*) are present. A [illegible] (*right side of illustration*) shows intimal fibrous tissue causing luminal narrowing. Capillaries are engorged. Proteinaceous material is in alveolar spaces. (Elastic tissue stain; original magnification ×23.) b, Dilatation of pleural and interlobular lymphatics (*L*). Edema of lung. (Elastic tissue stain; original magnification ×1[illegible].) c, A [illegible] showing concentric intimal proliferation causing luminal narrowing. (Elastic tissue stain, original magnification ×430.) d, A small [illegible] in receives [illegible] tributary. Each show[s] marked luminal narrowing by fibrous tissue. (Elastic tissue stain original magnification ×100.)

young adults. From reports of 31 cases, Wagenvoort found the range in age to be from eight weeks to 48 years, with an average of 19 years.

Pulmonary veno-occlusive disease is among three pathologic states that yield a clinical picture of primary pulmonary hypertension in which, characteristically, the pulmonary arterial wedge pressure is not elevated. The other two pathologic types of clinical primary pulmonar[y] hypertension are the plexogenic and thromboem[bolic] types. The plexogenic type of primar[y] pulmonary hypertension is first manifested as a[n] idiopathic vasospastic condition of the precapilla[ry] arterial vessels of the lung. At this stage, th[e] high levels of pulmonary vascular resistance th[at] give rise to increased pressure are labile, respond



Fig. 9 and b. a, A small pulmonary vein contains fibrous tissue in which there is a vascular space. The wall of the vein shows medial thickening suggesting arterial structure. (Elastic tissue stain, original magnification ×200.) b, Large muscular artery and small muscular arterial branch. Each shows medial hypertrophy without intimal disease. (Elastic tissue stain, original magnification ×100.)

ing to pulmonary vasodilatory drugs or inspiration of high concentrations of oxygen. At this stage, the anatomic change is that of medial hypertrophy of the muscular pulmonary arteries. As pulmonary hypertension is maintained, intimal changes like those seen in large ventricular septal defect appear. Among these lesions is the plexiform lesion from which this type of primary pulmonary hypertension derives its name. When plexiform and associated lesions appear, the pulmonary vascular resistance is of high order and the pulmonary hypertension is fixed.

The thromboembolic type of primary pulmonary hypertension is characterized by thrombi in various stages of organization, being present in the small pulmonary arteries. It is not known as to whether such thrombi have occurred *in situ* or represent embolism. Hence, the noncommittal term thromboembolism.

Wagenvoort considered the etiology of pulmonary veno-occlusive disease. While favoring an acquired condition in the form of thrombosis, he suggested that from one case to another there may be a varied background for this process. Such backgrounds might include coagulation abnormalities, viral or bacterial infection, toxic and even genetic factors.

Earlier in 1973, Liebow and colleagues, while considering the occlusive lesions to be derived from thrombi, stated that vascular disease as a causative factor had not been excluded. The condition appears to be different from the intimal fibrosis that involves congenital stenotic lesions of major pulmonary veins.

The relentless course followed by the patient described in this conference is in keeping with the experience of Rosenthal and associates. These authors found that in ten of 13 patients from whom complete clinical data were available and who died within two years after the onset of symptoms, the average survival was 20 months (range, one to 34 months).

In pulmonary veno-occlusive disease the location of the obstructive lesions and the secondary changes, such as pulmonary capillary engorgement, pulmonary edema, and dilatation of visceral pleural and pulmonary lymphatics, as observed in the case presented, may lead one to conclude that the pulmonary capillary pressure is elevated. Such a phenomenon as occurs in mitral stenosis is classically associated with elevated pulmonary arterial wedge pressures. As Dr. Ledbetter indicated in the case presented, it was not possible to obtain a pulmonary arterial wedge pressure. Judging from other cases, one may conclude that had such a pressure reading been obtained, it would not have been elevated.

The explanation of this seemingly paradoxical phenomenon in pulmonary veno-occlusive disease is that as the venules and small veins are

obstructed or occluded, the catheter wedged into a pulmonary artery is faced with a closed system. Once withdrawal of blood is done through the wedged catheter there is no head of pressure facing it.

DR. LEDBETTER Dr Edwards, could you tell us whether the pulmonary hypertension had been present from birth?

DR. EDWARDS Dr Gilbert described the pulmonary arterial media as exhibiting continuity of elastic fibers. This picture is present normally at birth and for several months thereafter There then follows a process of interruption of elastic fibers If pulmonary hypertension is maintained from birth the medial elastic fibers maintain their continuity In view of the observations in this case I would be of the opinion that pulmonary hypertension had been present either from birth or early infancy

The cystic medial necrosis of the pulmonary trunk that was also present is taken as a sign of pulmonary hypertension. Tredal and associates observed this process in pulmonary hypertension as seen in cases of large ventricular septal defect and in cases of acquired mitral stenosis.

Final diagnosis Pulmonary veno-occlusive disease.

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Fundamentals of clinical cardiology

Noninvasive diagnostic techniques in peripheral vascular disease

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Contrast arteriography and phlebography (venography) remain the standard diagnostic techniques for evaluation of peripheral arterial, cerebrovascular and venous diseases. However invasive angiographic techniques involve expense time, discomfort, and potential risks to the patient which preclude their use as routine screening and follow up procedures. These draw backs should not prevent appropriate application of angiography when necessary for planning therapy including operation. In order to obtain accurate objective information to complement the clinical diagnosis of peripheral vascular diseases, many noninvasive diagnostic techniques have recently become available to the clinician. The validity (sensitivity and specificity) of various noninvasive techniques is being established. It is incumbent upon the clinician to understand the principles, accuracy and limitation of these tests in order to make intelligent selection, application, and interpretation of these modalities in the diagnosis and management of patients with vascular disease.

The purpose of this paper is to review the currently available noninvasive diagnostic techniques for the evaluation of peripheral arterial, cerebrovascular and venous diseases. This paper will emphasize the principles, instrumentation, methods, applications, and results of these techniques. In addition, the attributes and limitations of each technique will be discussed, with emphasis on such factors as cost, portability simplicity accuracy and versatility of the instrument. Finally the structure and function of a noninvasive peripheral vascular laboratory will be reviewed, including attention to such details as space, practical equipment, personnel and financial structure of such a facility

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Techniques and applications

Doppler ultrasound

Principle. Doppler ultrasound detects blood flow by the frequency shift of ultrasound reflected from moving blood cells (Doppler effect) The instrument emits a beam of ultrasound, with a frequency of 2 to 10 MHz, from a piezoelectric crystal in the tip of a hand held probe. The ultrasound is transmitted into the tissues via an acoustic gel on the skin. Sound reflected from moving blood cells is shifted in frequency by an amount proportional to the blood flow velocity The back-scattered ultrasound is received by a second crystal and the frequency shift is detected and amplified by the instrument.

Instrumentation. Many commercial types of Doppler instruments are available, varying from small portable pocket-sized models to more sophisticated table-top instruments. Most detectors are continuous-wave devices which emit an ultrasound beam without interruption. Such devices are not range-specific that is, they will detect blood flow at any depth within the range of the instrument, up to several centimeters depending on the frequency of the instrument (the lower the frequency the greater the potential range of flow detection) Pulse-Doppler detectors transmit intermittent bursts of ultrasound which can be sampled for return signals at various times after transmission, permitting range resolution of detected flow at a given point from the transducer Most Doppler detectors are not *sensitive to*

the direction of the blood flow Directional Doppler detectors are capable of determining whether the frequency of the backscattered sound is above or below the transmission frequency permitting determination of flow toward or away from the Doppler probe. The output of Doppler instruments may be an audio signal (earphone or loudspeaker) an analogue tracing by means of a frequency to-voltage convertor (zero-crossing detector) or a sound spectral analysis of the audio frequency spectrum. In addition, some instruments (continuous or pulsed) which incorporate a position-sensing arm between the Doppler probe and a storage oscilloscope permit imaging of accessible vascular segments, such as the carotid artery by means of ultrasonic arteriography

Methods. Doppler ultrasound may be used for the following three purposes

1. Blood velocity signal analysis
2. Determination of systolic blood pressure
3. Vascular imaging

Velocity signal analysis is used in the assessment of peripheral arterial, cerebrovascular and venous disease. Systolic blood pressures permit semi-quantification of the presence, location, and functional extent of peripheral arterial occlusive disease. Doppler ultrasonic imaging is most useful to detect arterial occlusive disease of the carotid bifurcation.

Most commonly the *Doppler velocity signal* is [illegible]lyzed audibly using a stethoscope headset, earphones, or a loudspeaker Recently there has been an increasing trend to permanently record the blood velocity signals using an analogue tracing which is a voltage conversion of the audio frequency through a zero-crossing detector More complete representation of the many frequencies of the Doppler spectrum can be obtained by sound spectrum analysis, which is particularly useful in carotid blood velocity analysis. Assessment of *peripheral arterial disease*[3] is usually performed by analyzing the audible or analogue velocity signal at various points along the major arterial trunks. The normal peripheral arterial blood velocity signal is multiphasic with a prominent systolic component and one or more diastolic sounds. The first diastolic sound may be transient reverse flow which is a normal event in major peripheral arteries. Distal to an arterial stenosis or occlusion, the arterial blood velocity signal is attenuated with a less prominent systolic component and absence of the discrete diastolic sounds. At the site of stenosis the velocity signal is high pitched and occasionally turbulent in character In the presence of severe arterial occlusive disease with poor collateral circulation, the arterial velocity signal may be unobtainable. In the lower extremity the usual sites of arterial velocity evaluation include the common femoral, superficial femoral, popliteal posterior tibial, and dorsalis pedis arteries. In the upper extremity the subclavian, brachial, radial, and ulnar arteries are assessed. In some instances, the palmar arch and digital arteries may be examined.

In *cerebrovascular disease*[4] the periorbital arterial branches of the ophthalmic artery are routinely assessed for directional blood flow velocity and the influence of compression maneuvers on branches of the external carotid artery and each common carotid artery Normally the periorbital arterial flow direction is antegrade out of the orbit but it may be reversed in the presence of significant arterial occlusive disease of the extracranial internal carotid artery In such instances, the collateral circulation to the brain via the ophthalmic artery may be interrupted by compressing an appropriate branch of the external carotid artery Intracranial collateral circulation via the circle of Willis may be assessed by noting attenuation of periorbital arterial flow velocity in response to compression of the contralateral common artery The Doppler arterial velocity signal may also be assessed in each common carotid artery and its branches in the neck. Normally the common carotid artery carries increased flow velocity during diastole because of the low peripheral vascular resistance of the brain. In the presence of internal carotid artery occlusion, the common carotid artery signal may assume the characteristics of a normal peripheral artery Direct interrogation of the internal carotid artery with the Doppler probe permits assessment of turbulent signals in the presence of stenosis of this vessel. Sound spectrum analysis of internal carotid flow velocity permits sensitive detection of stenoses of approximately 25 per cent reduction in diameter a stage of disease not detectable by alterations in pressure or flow Such signal analysis is particularly useful in conjunction with Doppler ultrasonic imaging systems.

In *venous disease* the Doppler velocity signal has several characteristics which differentiate it

from the arterial signal. Normally venous flow velocity is of lower pitch and is phasic with respiration rather than with each heart beat. The signal may be augmented by compressing the limb distally or by releasing proximal limb compression. If the venous valves are competent proximal limb compression or a Valsalva maneuver will interrupt venous flow velocity. In the presence of venous thrombosis, these velocity characteristics are altered. The flow velocity may be absent or may become more continuous and little affected by respiration. Venous obstruction attenuates or prevents augmentation of flow velocity in response to limb compression maneuvers. Chronic venous insufficiency or varicose veins result in venous valvular incompetence with resultant reflux flow velocity signals in response to proximal limb compression or a Valsalva maneuver. The sites accessible for Doppler venous evaluation include the posterior tibial vein at the ankle, the popliteal, superficial femoral and common femoral veins in the lower extremity and the brachial, axillary, subclavian, and jugular veins in the upper extremity and neck. Indirect information is obtained from the iliac veins and the inferior and superior vena cava.

Determination of limb *systolic blood pressure* is the most simple and useful application of the Doppler in screening for peripheral arterial occlusive disease. The Doppler probe is used as a sensitive electronic stethoscope over an artery distal to a pneumatic cuff. The systolic blood pressure is determined at the point that the Doppler signal returns upon deflation of the cuff from suprasystolic pressures. The best technique to screen for peripheral arterial disease is to measure the ankle systolic blood pressure and relate it to the arm pressure as an *ankle/arm pressure index* (API). Normally the ankle pressure is equal to or higher than that of the arm (API $\geq$ 1.0). In the presence of arterial occlusive disease, the ankle pressure will be below that of the arm by an amount proportional to the degree of circulatory impairment. Patients with claudication normally have an ankle pressure index between 0.5 and 1.0. Patients with rest pain or gangrene usually have an API less than 0.5, with the absolute ankle pressure often less than 50 mm. Hg.

To localize arterial occlusive disease *segmental limb blood pressure*[1] may be determined. Specially designed pneumatic cuffs (inflatable bladders 12.5 × 40 cm) may be applied at the proximal thigh, above knee, below knee and ankle levels.[11] Although the relatively narrow cuffs result in some artifactual elevation of determined blood pressure, particularly on the thigh, such multi-segmental pressure measurements permit localization and regional semi-quantitation of arterial occlusive disease. Normally the proximal thigh pressure should be 20 to 30 mm Hg higher than that of the arm and there should be no greater than a 20 to 30 mm. Hg pressure gradient (artifactual) between adjacent levels of measurement on the leg. A low proximal thigh pressure signifies aorto-iliac or common femoral occlusive disease. An abnormal gradient between the proximal thigh and the above or below knee cuffs is indicative of superficial femoral or popliteal artery occlusive disease. An abnormal gradient between the below knee and ankle cuffs reflects tibioperoneal disease. In the upper extremity the arm and forearm pressures may be determined to detect an abnormal gradient associated with brachial artery occlusion.

Systolic blood pressure determination is useful to assess the functional impairment of the circulation during stress of the circulation or limb *hyperemia*. The best method to functionally assess arterial occlusive disease of the lower extremities is to measure the ankle pressure response to *treadmill exercise*.[11] A constant load test for five minutes at two miles per hour on a 12 per cent grade is normally tolerated without any drop in ankle pressure. In the presence of arterial occlusive disease, the patient may be unable to walk for more than one or two minutes and the ankle pressure will drop by an amount and duration proportional to the degree of circulatory impairment. In patients who cannot walk on a treadmill, a useful test of the circulation is to determine the ankle pressure response during *reactive hyperemia*[14] following temporary (3 to 5 minutes) ischemia induced by a thigh pneumatic tourniquet. Normally the ankle pressure will diminish by no more than 35 per cent below control levels and recover within 30 to 60 seconds. In arterial occlusive disease, the ankle pressure drop will be of greater magnitude (greater than 35 per cent drop) and duration, in proportion to the extent of arterial occlusive disease.

In carotid occlusive disease *Doppler ultrasonic arteriography* has become a potentially accurate

method to detect stenosis or occlusion of the extracranial internal carotid artery in the neck. Both continuous wave[illegible] and pulsed Doppler systems have been developed which translate the coordinates of detected blood flow velocity by means of a position sensing arm to a storage oscilloscope for subsequent recording of the built up vascular image on a Polaroid photograph. The advantage of such imaging systems over other noninvasive screening techniques is the fact that carotid stenosis (operable) can be differentiated from occlusion (inoperable) and milder degrees of stenosis may be detectable by the imaging technique. Calcification of the vessel wall may preclude satisfactory imaging and has led to the use of velocity signal analysis, including sound spectral techniques, for assessment of the distal internal carotid artery beyond the calcified nonvisualized segments.[illegible] Doppler imaging and flow velocity analysis may also be coupled with ultrasound B-scan techniques for carotid noninvasive arteriography.

Applications. In *peripheral arterial disease* the Doppler detector permits the assessment of the following (1) confirmation of diagnosis, (2) prediction of therapeutic result, (3) intraoperative monitoring, and (4) following of the natural history or therapy. The aforementioned techniques allow objective diagnostic *confirmation* of the presence location, and extent of arterial [illegible] e disease.[illegible] The usual techniques include [illegible]locity signal analysis from the major arterial segments, resting ankle pressure indices, segmental limb blood pressures and a hyperemia test, usually post-exercise. Such screening is particularly important in patients with ambiguous symptoms including those possibly due to orthopedic or neurologic conditions. In addition the Doppler is useful to screen patients with Raynaud's syndrome or other vasospastic states, assess the continuity of the palmar arterial arch, screen for arteriovenous fistula,[illegible] and rapidly assess patients who have suffered possible arterial trauma.[illegible] A particular type of iatrogenic arterial injury most suitably assessed by Doppler ultrasound is post-catheterization arterial obstruction, following femoral[illegible] or brachial[illegible] cardiac catheterization or peripheral arteriography.[illegible] Similarly the complications following insertion of indwelling arterial monitoring catheters can be readily screened with the Doppler detector. Finally the presence of significant arterial compromise in circumferential burns[illegible] or in the compartment syndrome[illegible] may be identified by Doppler ultrasound. Although not peripheral arterial diseases per se shock[illegible] and aortic valve stenosis[illegible] or insufficiency[illegible] may be noninvasively assessed by directional Doppler ultrasound.

Segmental limb blood pressures allow *prediction of therapeutic outcome* of aortofemoral[illegible] or femoropopliteal[illegible] reconstruction in patients with multisegmental arterial occlusive disease. Such pressures are also of predictive value in determining the likelihood of healing of amputations of the foot[illegible] or leg[illegible] of patients with advanced, unreconstructible arterial disease.

Intraoperative monitoring[illegible] of the integrity of femoropopliteal, carotid, and visceral arterial reconstruction involves assessment of arterial flow velocity signals using a gas-sterilized Doppler probe.[illegible] The change in ankle pressure index following aortofemoral reconstruction permits intraoperative prediction of the efficacy of the procedure in patients with multisegmental arterial occlusive disease.

Follow-up assessment of the natural history or results of therapy of arterial disease involves repeated measurement of resting and post-exercise (or reactive hyperemia) limb pressure. These data provide objective indices of disease progression and early or late complications of vascular reconstruction. Such information may permit therapeutic intervention prior to vascular or graft thrombosis that might jeopardize limb viability.

In *carotid artery disease* the periorbital Doppler examination will detect hemodynamically significant stenosis (≥50 per cent) or occlusion of the extracranial internal carotid artery with an accuracy of approximately 95 per cent as compared to contrast arteriography. However this accuracy is only achieved if a complete examination is performed, including compression maneuvers of all branches of the external carotid artery as well as each common carotid artery. The technique is not sensitive to non-obstructing lesions including ulcerated plaques that do not significantly narrow the lumen. Thus, the technique is not suitable for detecting operable lesions of symptomatic patients with transient ischemic attacks or recovery from stroke.[illegible] It is estimated that approximately 50 per cent of all patients who are candidates for carotid endarterectomy will have a normal periorbital Doppler examination.[illegible]

Furthermore an abnormal examination does not distinguish between an operable stenosis and an inoperable occlusion. Such differentiation is important and may be carried out with an experienced direct carotid Doppler examination in the neck, with or without ultrasonic imaging of the carotid bifurcation. The conventional periorbital Doppler examination is of value in identifying hemodynamically significant carotid disease in patients with asymptomatic bruit, clarifying the etiology of patients with ambiguous cerebral symptoms such as dizziness, headache or syncope, and following the natural history of carotid occlusive disease including the long term effect of medical or surgical management. In addition, a sterilized Doppler probe may be used to directly assess the carotid bifurcation at the conclusion of carotid endarterectomy. Furthermore, an intraoperative periorbital Doppler examination is useful to assess the integrity of the carotid circulation at the time of operation. Finally the periorbital Doppler examination permits indirect estimation of the hemispheric collateral perfusion pressure,[48] by noting the direction of ophthalmic artery flow during the period of transient common carotid compression.

In *venous disease* the Doppler examination provides an accurate assessment of obstruction or valvular incompetence of the deep and superficial venous systems. In experienced hands, the technique permits identification of major deep vein thromboses with an accuracy of 95 per cent as compared to contrast phlebography.[49, 50] The technique is also sensitive to major thrombi limited to the calf veins. However the technique requires considerable experience and attention to technical details.[19] The method permits versatile assessment of the venous system not possible with other noninvasive techniques. Both the upper and lower extremities and the jugular venous system may be examined. The technique permits differentiation of superficial[51] and deep venous disease and is an accurate guide to chronic venous incompetence of the deep,[52] perforating,[53] and superficial veins. The method may be applied to patients in traction or plaster casts and patients with amputations may be evaluated.[54]

Attributes and limitations. The Doppler ultrasonic velocity detector is the least expensive (as low as $250) and most versatile of all of the available noninvasive diagnostic techniques to assess peripheral vascular diseases. The device may be as small as a large penlight, is portable, and may be used rapidly by an experienced technologist. The use of Doppler ultrasound in peripheral arterial disease is as relatively simple and straightforward as measuring a standard blood pressure. Cerebrovascular evaluation requires more experience and venous evaluation depends to the greatest degree upon the skill and experience of the examiner. The technique requires some subjective interpretation of the character of flow velocity signals which are usually audibly interpreted by the observer. However analogue tracings may be readily recorded for a permanent hardcopy record of the examination. With experience a technologist may achieve approximately 95 per cent accuracy in detecting peripheral arterial, cerebrovascular or venous disease with this instrument. In general, the sensitivity of Doppler ultrasound to arterial and venous disease is restricted to those lesions which result in hemodynamically significant impairment to blood flow, i.e., 50 per cent or greater reduction in diameter of the vascular lumen. Thus, mild atherosclerotic plaques and small venous thrombi may be overlooked with the technique.

B-scan ultrasound.

Principle. This technique graphically records cross-sectional anatomy on a storage oscilloscope by means of detected reflected echos of ultrasound at various tissue interfaces within the range of the instrument. Standard units use two MHz (abdomen) while special B-scan devices may operate at higher frequencies (five MHz for carotid imaging, ten MHz for ocular imaging). The instrumentation is similar to that of Doppler ultrasonic arteriographs with the exception that the detected information is a static echo rather than a Doppler frequency shift.

Instrumentation. Many off line as well as real time B-scan ultrasonic imaging devices are available, particularly for abdominal, obstetric, and other uses. An abdominal B-scan unit is useful in peripheral vascular disease to visualize the morphology of the abdominal aorta in screening for abdominal aortic aneurysm.[57] The same technique may be used on more distal blood vessels to assess femoral or popliteal aneurysms.[58] Recently real-time B-scan devices have been developed to image the carotid bifurcation in the neck.[59] A combination of B-scan and Doppler imaging (duplex scanner) has provided excellent morpho-

logic and hemodynamic assessment of the carotid bifurcation.[71]

Methods Currently the use of B-scan devices in peripheral vascular disease is limited to morphologic assessment of arterial aneurysms and screening for carotid occlusive disease. The techniques are similar to other B-scan applications and will not be discussed in detail in this paper Gray scale techniques permit increased enhancement of aneurysm content including thrombosis or atherosclerotic plaque In carotid imaging, problems similar to that with Doppler arteriography are present when extensive calcification of the arterial wall exists. Acoustical shadows may occur and limit visualization, particularly of the artery wall opposite the calcified area. Combinations of B-scan imaging and Doppler velocity analysis are useful to increase the diagnostic accuracy in carotid occlusive disease.

Application and results. B-scans are useful to distinguish an abdominal aneurysm from a tortuous aorta. Such differentiation may be difficult in the obese patient by clinical palpation alone. The estimation of the transverse and anterior posterior diameter of the abdominal aortic aneurysm is usually very accurate by this method and exceeds the accuracy of conventional radiography and arteriography The accurate assessment of an abdominal aortic aneurysm size is useful in following the natural history of the ...ysm in patients who are not suitable candidates for operation Similarly B-scan of the popliteal space may permit differentiation of a popliteal aneurysm from a Baker cyst or other mass of the popliteal fossa. In carotid imaging, the application is similar to that mentioned above under Doppler ultrasonic arteriography Both B-scan and Doppler techniques, or their combination in the duplex scanner permit not only conventional longitudinal images in the projection mode but also unique cross-sectional views of the carotid artery and its branches.

Attributes and limitations. The greatest attribute of both B-scan and Doppler ultrasonic imaging is the fact that a morphologic depiction of the arterial disease is possible, in a manner that is generally interpretable by most physicians. With experience the technique can very accurately describe the presence and size of an arterial aneurysm. The devices do permit a hard-copy record of the procedure The carotid imaging may become the most useful and sensitive way to detect carotid occlusive disease however the technique may result in false-positive diagnosis as a result of vascular wall calcification. The drawbacks to imaging techniques include their expense and relative large size that limits portability The imaging techniques are somewhat complex and require an experienced technician and a knowledgeable physician for their performance and interpretation. While a B-scan device may be versatile in imaging various portions of the body the carotid imaging devices have a more restrictive application primarily in carotid occlusive disease.

Plethysmography

Principle. The plethysmograph (to record an increase") provides graphic recordings of a change in dimension of a portion of the body in response to each heart beat or in response to temporary obstruction of venous return (venous occlusion plethysmography)[**] Most plethysmographs record directly or indirectly the change in volume of the digit limb, or other part of the body An exception to this is the photoplethysmograph[**] which records a change in reflection of light from the change in the number of red blood cells in the cutaneous microcirculation.

Instrumentation There are five different types of plethysmographs currently in use for evaluating peripheral vascular disease. Each type employs a different transducer principle for recording the changes in body dimension. The *water* plethysmograph[**] is one of the oldest methods of recording limb or digit volume using the displacement of water as the means of recording changes in limb girth. The technique has been widely used by physiologists but the instrument is bulky cumbersome, and impractical for routine clinical use. A water filled device has been developed for use as an ocluar plethysmograph (OPG)[*] for screening for carotid occlusive disease The photoelectric or photoplethysmograph (PPG)[*] has been used for many years as a pulse sensor This technique employs a tungsten light source or more recently an infrared light emitting diode[*] to transmit light into skin. Light reflected from blood cells is received by a photocell or phototransistor which permits recording of the pulsatile cutaneous microcirculation. Recently this technique has proved useful to screen for peripheral arterial,[**] cerebrovascular[**] and venous disease. The *strain gauge plethysmograph* (SPG) employs the principle of the change in

resistance of a column of mercury in an elastic gauge as a sensor of digit or limb volume as originally described by Whitney.[68] This technique is extremely simple and versatile for screening for peripheral arterial and venous disease. Recent modifications of the instrument have permitted electrical calibration of the gauge *in situ* on the limb,[69] automatic calculation of limb flow from the excursion of a panel meter needle,[70] and self-calibration of gauges of different lengths.

The *air plethysmograph* has been used in a variety of instruments, including the oscillometer the Dohn[72] and Winsor[73] plethysmographs, and the pulse volume recorder (PVR) all of which have been used extensively for peripheral arterial disease. The latter three devices have also been used for venous evaluation. A more specific and detailed technique for evaluating venous disease by air plethysmography is the phleborheograph (PRG).[75] Finally an air filled oculopneumoplethysmograph (OPG)[76] has been developed to screen for cerebrovascular disease and to estimate hemispheric collateral perfusion pressure. The *impedance* plethysmograph (IPG)[77] has been extensively used for detection of acute deep vein thrombosis. The technique employs measurement electrodes which sense changes in a minute electric current sent through a portion of the body by means of separate electrodes proximal and distal to the sensing electrodes. The change in electrical impedance of the portion of the body is a reflection of the change in blood content associated with each heart beat or in response to temporary venous occlusion. The latter technique is the method by which the device assesses deep vein thrombosis.

Methods. Plethysmographic techniques permit assessment of peripheral vascular disease by one of the following three techniques

1. Pulse wave analysis
2. Determination of digit or limb blood pressure
3. Determination of arterial or venous blood flow

Pulse wave analysis is particularly useful in peripheral arterial and cerebrovascular evaluations. Assessment of digit or limb blood pressure permits semi-quantitation of peripheral arterial occlusive disease. Assessment of limb blood flow permits quantitation of peripheral arterial and venous disease.

In *pulse wave analysis*, the contour and amplitude of the plethysmographic pulsation with each heartbeat is a qualitative guide to the presence and degree of peripheral arterial occlusive disease. Normally the pulse wave has a steep upslope, a relatively narrow peak, and a dicrotic wave on the downslope which is concave toward the baseline. In the presence of arterial occlusive disease the pulse wave contour is damped with a more gradual upslope, a broad rounded peak, and loss of the dicrotic wave on the downslope which becomes convex away from the baseline. The amplitude or height of the pulse wave progressively diminishes with increasing arterial obstruction. The amplitude will also decrease in response to a sympathetic discharge, such as that induced by a deep breath or by mental arithmetic. Such a test is a useful index of the presence of intact sympathetic vasomotor tone. Pulse amplitude reduction is also noted in tests of palmar arterial arch continuity and in response to maneuvers which may compress the thoracic outlet. Finally the capacity of the peripheral arterial system to vasodilate may be assessed by noting the increase in digit pulse amplitude in response to reactive hyperemia following deflation of an occlusive arterial tourniquet. In cerebrovascular disease, the water filled ocular plethysmograph (OPG) permits assessment of delay in filling of the globe of the eye in the presence of hemodynamically significant carotid arterial occlusive disease.[43] In venous disease, the air filled phleborheograph (PRG) permits segmental leg recording of attenuations of the normal fluctuations of limb volume with respiration and abnormal changes in limb dimension during foot or leg compression maneuvers.

Digit and segmental limb *systolic blood pressures* may be determined by means of a plethysmograph.[13] Such pressure determinations are more simply carried out by Doppler ultrasound. However the measurement of digit blood pressure usually requires a plethysmograph transducer on the distal phalanx.[79] Photopulse, strain gauge, or air transducers are suitable for detecting the return of pulsations following deflation of a specially-designed blood pressure cuff. Such digit pressure measurements are particularly useful in patients with diabetes mellitus, Raynaud's syndromes, and advanced peripheral arterial occlusive disease.

Determination of digit or limb *blood flow* by plethysmography provides the most accurate

quantification of peripheral arterial or venous disease. Generally measurement of limb blood pressure is a more simple and convenient technique of semi-quantitating peripheral arterial occlusive disease. However limb or digit blood flow may be determined by means of venous occlusion plethysmography from the rate of initial increase in limb or digit circumference in response to temporary venous occlusion with a proximal pneumatic cuff.[47] The limb blood flow may remain normal in peripheral arterial occlusive disease until the disease becomes far advanced. Thus, it is necessary to measure the abnormal attenuation of the increase in limb blood flow during stress, such as that during reactive hyperemia or following limb exercise.[48] Normally arterial blood flow increases by several times the resting level during hyperemia, and rapidly returns to normal within a few seconds (reactive hyperemia) or in one or two minutes (post-exercise hyperemia). In the presence of arterial occlusive disease the hyperemia will be attenuated and prolonged in proportion to the degree of the circulatory obstruction.

Assessment of the rate of decrease in limb circumference following a period of venous occlusion is an index of the patency of the deep venous system. Such graphic measurement of venous outflow is a basis of detection of deep vein thrombosis by water,[42] strain gauge (SPG), impedance (IPG) or air (PVR) plethysmographic techniques. The strain gauge and photoplethysmograph (PPG) also permit quantification of abnormalities of venous reflux following pneumatic cuff inflation[44] or by exercise[4] in patients with post-phlebitic venous incompetence[43] or varicose veins.[45, 46]

Applications and results. In *peripheral arterial disease* digit and limb plethysmography provide a graphic record of the presence and extent of peripheral arterial occlusive disease. It has not been established whether segmental limb plethysmography provides any additional information to that available from measurement of segmental limb blood pressures and arterial velocities by Doppler ultrasound. However plethysmography does provide valuable information about the status of the digit circulation, particularly in patients with distal or advanced arterial occlusive disease. In addition the technique permits assessment of the presence of peripheral sympathetic tone which may influence the decision to perform lumbar sympathectomy,[49] which seldom is of significant benefit in arterial occlusive disease. Plethysmography is useful to distinguish digit vasospasm in Raynaud's disease from the digit arterial occlusive lesions of Raynaud's phenomenon.[50] Digit plethysmography also provides graphic assessment of the patency of the palmar arterial arch and the presence or absence of thoracic outlet compression. Finally plethysmography permits assessment of the abnormal arterial hemodynamics in patients with acquired or congential arteriovenous fistula.[15]

In *cerebrovascular disease* several types of plethysmographs have been applied for detection of significant stenosis (≥50 per cent) or occlusion of the extracranial internal carotid artery. The water filled ocular plethysmograph (OPG)[51] has been most widely employed to detect significant carotid occlusive disease on the basis of a delay in ocular pulsation relative to that of the opposite eye and the ear. The technique has also been used in conjunction with carotid phonoangiography to be described later. In experienced hands, the technique is associated with a sensitivity and a specificity of approximately 90 per cent each in detecting or excluding significant arterial occlusive disease of the extracranial internal carotid artery as established by contrast arteriography. The method requires ocular anesthesia and can be performed by an experienced technologist in approximately ten minutes. Recently an air filled device which employs a computer to automatically calculate ocular pulse delay from a sequential number of pulse beats, has been developed. The air filled oculopneumoplethysmograph was originally designed to estimate the collateral hemispheric perfusion pressure.[52] The technique records the return of ocular pulsation while gradually decreasing a vacuum applied to the ocular transducer. This technique is useful to determine the status of the collateral hemispheric circulation during common carotid compression in patients who may require sacrifice of the internal carotid artery. Recently the technique has been modified to permit screening for the presence of significant carotid artery occlusive disease.[53] The photoplethysmograph (PPG)[54] provides a simple monitor of supraorbital pulse amplitude during sequential compression of branches of each external carotid artery and each common carotid

artery. Abnormal attenuation of supraorbital pulsations is indicative of significant extracranial carotid occlusive disease. Supraorbital photoplethysmography detects hemodynamically significant carotid occlusive disease with an accuracy of approximately 95 per cent compared to contrast arteriography. The technique is extremely sensitive but false-positive results may occur leading to a specificity of approximately 90 per cent.[64]

In *venous disease* a variety of plethysmographic techniques may be employed to detect acute deep vein thrombosis. Many techniques, including water[65] strain gauge,[66] impedance[67] and air techniques measure the rate of decrease in calf circumference in response to deflation of a veno-occlusive thigh cuff. An abnormal recording of venous outflow signifies significant venous obstruction at or proximal to the level of the popliteal vein. These techniques have an accuracy approaching 95 per cent in detecting or excluding major leg vein thrombosis. The phleborheograph (PRG)[71] assesses limb venous hemodynamics on a different principle, somewhat similar to that of Doppler ultrasound. The technique involves multiple segmental limb pneumatic cuffs which are used as air plethysmographs to measure segmental limb volumetric responses to breathing as well as to limb compression maneuvers. Detection of superficial or deep venous valvular incompetence in varicose veins or postphlebitic stasis disease may be documented plethysmographically with the strain gauge, photopulse, or phleborheographic techniques. Strain gauge plethysmography permits documentation of abnormal venous reflux in response to thigh pneumatic compression below a proximal tourniquet.[14, 72, 73] More simple techniques involve recording of abnormal calf volumetric responses to muscular exercise using a strain gauge plethysmograph[74] or a photoplethysmograph in a direct-current mode.[75]

Attributes and limitations. Plethysmographs have the advantage of an objective record of the vascular evaluation which can be readily carried out by a technician with modest experience. Most plethysmographs are portable and relatively simple to operate. With experience the accuracy of detecting vascular disease may approach 95 per cent. Drawbacks to plethysmography include greater cost, ranging from $500 to $10,000, and limited versatility of many of the instruments.

Phonoangiography

Principle. This technique involves graphic recording of vascular bruits associated with arterial stenosis, with or without analysis of the frequencies of the detected sound.

Instrumentation. Phonoangiography has generally employed the oscillographic recording of the amplitude of an arterial bruit with respect to time, using a Polaroid photograph of the image obtained on a storage oscilloscope.[44] More sophisticated techniques have involved frequency analysis of the components in the spectrum of the bruit [77] using Fourier analysis or other techniques to characterize the bruit. Such techniques permit more specific diagnosis of the severity of the arterial obstruction.

Methods. The conventional method to record arterial bruits is the frequency-time oscillographic plot using an electronic microphone which is positioned over the course of the artery to be studied. The most useful application is in carotid occlusive disease to identify the characteristics of a carotid bruit. Using frequency amplitude plots by means of sound spectral analysis, the severity of a carotid stenosis, within one millimeter may be estimated.

Application and result. The carotid phonoangiograph (CPA) has been used in conjunction with the water filled ocular plethysmograph (OPG) to screen patients for hemodynamically significant carotid occlusive disease.[44] This technique is about 85 per cent accurate in identifying hemodynamically significant obstruction of the carotid artery and its branches. Phonoangiography is particularly useful to distinguish bruits radiating from the thorax or subclavian arteries from carotid bifurcation bruits. In addition, the technique may specifically identify severe internal carotid artery stenosis when the bruit extends into diastole. Finally phonoangiography is helpful in detecting bilateral carotid occlusive disease of equal severity which may not result in pulse delay determined by ocular plethysmography.

Attributes and limitations. The carotid phonoangiograph (CPA) is relatively rapid and simple to use by an experienced technologist. The technique provides a graphic record of the presence and location of a carotid bruit. The sensitivity and specificity of this technique are less than that of other noninvasive diagnostic techniques, inas-

much as total occlusion may not be associated with a bruit and a stenosis of the external carotid artery may be the cause of a detected bruit. The instrument is fairly expensive, approximately $2,700 and its application is limited to carotid and peripheral arteries involved by stenosis.

Radioisotope techniques.

Principles. A variety of vascular diagnostic techniques have been developed which involve the injection of a small amount of radiopharmaceutical and subsequent detection of blood flow depot washout, or particle distribution by means of an external scintillation detector

Instrumentation. A number of different radioisotope detection techniques may be used to screen for peripheral arterial, cerebrovascular or venous disease. Some techniques involve small portable hand held scintillation detectors, whereas other techniques involve large stationary detectors and imaging systems as part of a nuclear medicine laboratory

Methods. There are four techniques involving radioisotopes that are useful in peripheral vascular disease

1. I 125 fibrinogen scanning for active venous thrombosis.
2. Radionuclide angiography and scanning for peripheral arterial, cerebrovascular and venous disease
3. Xenon 133 washout determination of arterial blood flow
4. Radioactive microsphere assessment of regional blood flow and arteriovenous shunting.

The *I 125 fibrinogen scanning* technique[*] involves detection of excess uptake of injected labelled fibrinogen at sites of active venous thrombosis in the lower extremity The technique is particularly sensitive to thrombosis, even minute, in calf popliteal, and distal femoral veins. The technique has been widely employed in prospective surveillance studies of venous thrombosis in high risk patients.[**] Inasmuch as the technique requires repeated scanning of the legs on several successive days, the method is less applicable to routine screening of patients with suspected active leg vein thrombosis. The technique is not sensitive to thrombi which are no longer actively forming

Radionuclide angiography involves injection of sodium pertechnetate o other radionuclide intravenously wit imaging f the radioactive particles in the venous system (radionuclide phlebography)[**] or in the major arteries (radionuclide arteriography) following circulation through the lungs. In cerebrovascular disease the technique provides gross assessment of arterial flow in the dynamic flow phase and subsequent brain scanning may be performed.[**] In venous disease the use of radionuclide-labelled particles of albumin permits imaging of the venous system in the lower extremities and subsequent perfusion lung scanning.[**]

The *Xenon 133 washout* technique is a useful method to determine discrete muscle compartment blood flow [**] The technique involves injection of approximately 50 microcuries of Xenon-133 dissolved in saline into the muscle with subsequent recording of the rate of washout of the isotope from the site of injection. Xenon 133 freely crosses the capillary endothelium and the rate of washout is directly proportional to capillary blood flow This technique has been predominately employed in clinical investigation of peripheral arterial disease and compartment compression syndromes.

The use of *radioactive microspheres*[**] has permitted assessment of regional distribution of blood flow particularly in patients with advanced arterial occlusive disease or ischemic ulceration. Radionuclide-tagged particles of albumin are injected intra arterially and the distribution of the radioactive particles may be determined by scanning of the extremity The technique detects areas of poor perfusion. The degree of radioactivity of tissues surrounding an ischemic ulcer is an accurate guide to the healing potential of the lesion. Microspheres also permit assessment of the degree of arteriovenous shunting, [**] which is of particular importance in assessing the hemodynamic results following lumbar sympathectomy [**]

Application and results. In *peripheral arterial disease* radioisotope techniques primarily have been helpful in clinical investigation of severe arterial occlusive disease. The Xenon 133 washout technique permits determination of regional muscle blood flow at rest and during hyperemia following temporary ischemia or following exercise [**] The technique has also been used to determine cutaneous blood flow in the lower extremity to predict the healing potential of a given level of amputation [**] Xenon 133 washout

determinations are also of specific value in deter mining circulatory compromise in muscle com partments involved by circumferential burns,[*] electrical injury [*] or by compartment-compres- sion syndromes.[11] Radionuclide arteriography has been employed to distinguish abdominal aortic aneurysm from torturous aorta,[*] although B-scan ultrasound has largely replaced this tech nique. The method is also useful to screen for arterial trauma[*] and to assess renal transplant function.[*]

In *cerebrovascular disease* dynamic and static radionuclide scans are routinely used to screen for carotid occlusive disease and to assess the integri ty of the blood–brain barrier.[*] The Xenon 133 washout technique has been used extensively to assess regional cerebral blood flow.[*] Recent advances in this technique, using intravenous or inhalation methods rather than carotid injection, may increase the applicability of Xenon 133 washout in determining cerebral perfusion.[*] Radionuclide microspheres have been used exper imentally to determine carotid ulceration, although clinical investigation of this technique has not yet been carried out.

In *venous disease* I 125 fibrinogen leg scanning has been most extensively used to detect active leg vein thrombosis. The technique has been applied in two circumstances.

1. Prospective expectant surveillance of pa tients at risk of developing leg vein thrombosis.
2. Diagnostic screening of patients with clinical manifestations of acute leg vein thrombosis.

Most previous reports emphasized the expec tant application of the technique particularly in patients undergoing major surgical procedures.[*] Prospective screening with I 125 fibrinogen leg scanning has resulted in an incidence of detected leg vein thrombosis of 10 to 50 per cent of patients in such high-risk categories as major abdominal surgery hip surgery and resection of prostatic malignancy The over all accuracy of I 125 fibrin ogen leg scanning compared to contrast phlebo- graphy[*] is approximately 90 per cent, although the extreme sensitivity of the technique may permit detection of minute leg vein thrombi which may not be visualized with conventional phlebography However false negatives may oc cur if the thrombotic process is no longer active or involves proximal areas of the thigh or pelvis which are not accessible to leg scanning. The use of I 125 fibrinogen leg scanning for diagnosis of patients with clinically suspected disease is of limited value because of the time required for repeat daily scanning in order to establish the diagnosis.[*]

Radionuclide phlebography is useful to rapidly assess the status of the major deep veins at and above the level of the popliteal vein.[*] The tech- nique is no different from that employed in routine lung or brain perfusion scanning. The technique provides images of the major deep veins with excellent visualization of intra abdominal veins despite peripheral injections in the feet. The technique is rapid and the injections are painless. Major venous thrombosis may be detected with an accuracy of approximately 90 per cent compared to contrast phlebography The use of radionuclide-tagged particles permits subsequent perfusion lung scanning following the dynamic phase of the phlebogram.[*]

Other radionuclide techniques of evaluating venous disease include the use of radioactive- tagged streptokinase or other agents which become attracted to thrombi and permit visual ization of areas of increased activity at the sites of venous thrombosis. The advantage of such tech niques is that thrombi may be localized even though they are inactive and would be overlooked by conventional I 125 fibrinogen leg scanning. Only a limited clinical investigation of such tech niques has been carried out. Finally radionuclide studies have been performed to functionally assess the calf venous muscle pump dynamics in patients with chronic venous insufficiency Such techniques are rather cumbersome and are less clinically applicable than plethysmographic or Doppler ultrasonic methods of evaluating chronic venous insufficiency

Attributes and limitations. The advantages of radionuclide techniques include their objectivity and accuracy in detecting either active thrombi or in visualizing major venous thrombi. The tech niques may be readily carried out with the facili- ties of conventional nuclear medicine depart ments. However the techniques are relatively expensive, require the use of radioactive materials and, with imaging systems, are not portable. The techniques require the availability of highly trained technicians, as well as physicians skilled in nuclear medicine techniques. However I 125 fibrinogen leg scanning remains the only tech

nique which is sensitive to the activity of venous thrombosis, which may be particularly important in evaluating patients with suspected recurrent venous disease. Furthermore radionuclide phlebography is the only technique which permits rapid and relatively painless visualization of major venous thrombosis, compared to contrast phlebography. These techniques remain limited to major hospitals and are not to be considered components of the standard noninvasive peripheral vascular laboratory.

Miscellaneous techniques. Thermography has been employed for evaluation of peripheral arterial, cerebrovascular and acute or chronic venous disease. The technique involves a special thermal detector which is sensitive to infrared light emitted from the surface of the body. The method functions on the principle of comparing the thermal temperature of various areas of the body to detect areas of abnormal coolness, such as the legs in peripheral arterial disease or the forehead in cerebrovascular disease, or areas of abnormal heat such as the legs in acute deep vein thrombosis or post phlebitic incompetence of perforating veins. The limitations of the technique include its expense, size complexity and nonspecificity which preclude its use as a routine diagnostic technique in the peripheral vascular laboratory.

Ophthalmodynamometry [16] is a screening test for cerebrovascular disease that indirectly deter the intraocular systolic and diastolic pres- res from a scaled compression tonometer lied to the eye, by noting the initial appearance and the maximal excursion of retinal arterial pulsations as viewed by an ophthalmoscope. The technique may be readily performed by an ophthalmologist. In experienced hands, the technique detects significant carotid occlusive disease with an accuracy of approximately 85 per cent when compared to contrast arteriography. However the method may result in false negative diagnoses in the presence of excellent collateral circulation to the eye and the technique may not detect bilateral carotid occlusive disease of equal severity. A variation of the technique compression tonography [17] involves recording of ocular pulsations during transient carotid compression. This technique has resulted in increased accuracy and is similar to other ocular plethysmographic techniques in the ability to detect hemodynamically significant carotid occlusive disease.

Recently *hematologic techniques* have been increasingly employed to characterize the coagulation and platelet function of patients with arterial or venous thrombosis. These techniques will not be reviewed in this paper except to indicate the importance of determining coagulation and platelet abnormalities in patients who are subject to recurrent arterial or venous thrombosis.

Other laboratory equipment. In addition to the aforementioned techniques, a well-equipped vascular laboratory will require other support equipment and supplies. Perhaps the most useful device will be a *recorder* to record the d-c signals associated with Doppler ultrasound or plethysmographic examination. The conventional electrocardiograph recorder may be used, but dedicated peripheral vascular laboratories will usually benefit from the availability of a special recorder for the noninvasive techniques. A two-channel recorder is particularly helpful to permit recording of bilateral leg plethysmographic tracings. A two-channel recorder also permits separate recording of forward and reverse flow velocity signals by directional Doppler ultrasound. Many of the commercially available Doppler ultrasound and plethysmographic devices include a suitable recorder for providing permanent hard-copy tracings of the diagnostic studies. Depending upon the number of channels, paper speeds, and options, a recorder may cost from $1,000 to several times this amount.

A *treadmill* is helpful to provide reproducible exercise testing of patients with peripheral arterial occlusive disease. Inasmuch as constant load tests are routinely performed in peripheral vascular laboratories, a treadmill with multiple speeds and variable elevation is not mandatory. Basic treadmills with a two-speed option and two levels of elevation may be purchased for approximately $2,000. The advisability of electrocardiographic monitoring during treadmill testing for peripheral vascular disease is controversial. Because the constant load test is not a major stress to the patient, and indeed is no more than the usual activity of the patient, ECG monitoring has not been routinely practiced in the past. However there have been rare instances of myocardial ischemia or infarction during constant load treadmill testing of patients with peripheral arterial occlusive disease. Any patient with a history of

angina pectoris should undergo treadmill testing in the conventional stress ECG laboratory with full monitoring during the constant load test. Inasmuch as the patients with peripheral arterial occlusive disease may have asymptomatic coronary artery disease, the peripheral vascular laboratory may consider the advisability of routinely monitoring the electrocardiogram during constant load testing of such patients. Such monitoring equipment, including an oscilloscope will approximately double the cost of the treadmill.

Other miscellaneous supplies include a hand held manometer and specially-designed pneumatic cuffs with bladders sufficiently long to encircle the leg for segmental pressure measurements. In order to facilitate measurement of segmental limb pressures and to provide rapid inflation and deflation of pneumatic cuffs during venous occlusion plethysmography an automatic cuff inflator operating on compressed air from a wall outlet or a self-contained compressor may be of value.

Finally an examination table or bed will be required, for most of the non invasive diagnostic studies are performed with the patient supine. The table should have a comfortable mattress. For plethysmographic studies of venous outflow in evaluation of venous disease, elevation of the lower extremities is required. The most simple arrangement for such studies is the use of the foot gatch with knee flexion, using a standard hospital bed. Such a bed, with electrical controls, makes a suitable all-purpose examination bed for a laboratory and should be placed in a room such that the technician can move about on all sides of the bed for the various diagnostic examinations.

The noninvasive peripheral vascular laboratory

Space. Although many of the aforementioned diagnostic techniques may be carried out on a portable basis by an experienced technologist, a dedicated space for a noninvasive diagnostic laboratory permits the greatest efficiency and versatility of this facility. A room with a floor space of approximately 200 sq ft. is adequate for a routine laboratory. Obviously the size of the facility will depend on the number of diagnostic studies performed. Large institutions with a heavy caseload of diagnostic vascular studies may require several rooms for efficient operation. In such instances, separate rooms dedicated to peripheral arterial, cerebrovascular and venous studies permit optimal use of equipment dedicated to a given diagnostic function. Space is also necessary for a desk and file for the technologist.

Equipment. With the many types of available instruments for noninvasive evaluation of peripheral vascular disease, the physician may be overwhelmed by the choices and have difficulty in deciding upon the most practical equipment for his individual needs. Unfortunately there is no simple solution to this dilemma, although most physicians initiate a laboratory with relatively inexpensive and versatile equipment and gradually add new devices as their experience and understanding of the techniques grow. Probably the most useful and versatile device to initially purchase for the laboratory is a Doppler ultrasonic velocity detector. Such a device will be readily applied in peripheral arterial disease and, with experience, will provide useful diagnostic information in cerebrovascular and venous diseases. For increased objectivity and accuracy the purchase of a plethysmograph is advisable, and some of the devices permit versatile assessment of arterial and venous disease. Such equipment also provides recording capability. Finally a treadmill is recommended for most active vascular laboratories involved in evaluating peripheral arterial occlusive disease.

Personnel. The *physician* who supervises or directs the noninvasive peripheral vascular laboratory must have a vested interest in vascular disease. Some physicians may have broad interest in peripheral arterial, venous, and cerebrovascular disease, such as the vascular cardiothoracic, or general surgeon, internist, or family practitioner. Other physicians may have more specific interest in one or two areas of vascular disease, such as the cardiologist, neurologist, ophthalmologist, hematologist, or orthopedic surgeon. Regardless of the background and interest of the given physician, he must maintain a continuing and up-to-date interest in diagnosis and management of vascular disease. While physicians may wish to personally perform some of the diagnostic studies, the most efficient application of noninvasive vascular diagnostic testing is performed by an experienced technologist. The physician's role must be one of guidance and interpretation of the activities of the laboratory. The physician must place the appropriate selection and interpretation of the noninvasive diagnostic information into perspective in the over all diagnosis and manage-

ment of the patient. The clinician must recognize the attributes and limitations of the various diagnostic techniques and not place too much weight upon the laboratory data to the exclusion of important information from the history physical examination and angiogram

The *technologist* serves a key role in the operation of the noninvasive peripheral vascular laboratory This individual may have one of several backgrounds, although the nurse-specialist is particularly suited in this role of balancing patient interaction with technical activity The technologist has a broad and challenging responsibility for scheduling of patients, obtaining baseline, historical and examination data performance of a variety of diagnostic technical procedures, recording and preparing data for reporting forms, assisting in interpretation of the information, and distributing and filing of the accumulated data. This individual also must become skilled in routine maintenance and service of diagnostic equipment as well as managing an appropriate supply inventory

The *education* of the vascular laboratory technologist as well as the responsible physician is a challenging problem. Within the past few years there has been increasing attention to inclusion of sessions on noninvasive vascular techniques in connection with national meetings, as well as separate workshops or seminars dedicated to this new area of medical practice. With increasing diagnostic techniques, further spread of these educational curricula will ensue The specific training of the laboratory technologist remains varied, with preceptorships with practicing physicians or visits to active laboratories being the usual method of learning the diagnostic skills. The development of programmed audio-visual instructional materials and the establishment of regular educational workshops in experienced centers, similar to training programs in other diagnostic areas of medicine, are anticipated future objectives of transferring these skills to medical practitioners. The development of associations such as the Society for Noninvasive Vascular Technology will play an important role in enhancing interest in education in noninvasive vascular procedures.

Purpose. The most obvious function of the noninvasive peripheral vascular laboratory is the provision of diagnostic services for the evaluation of patients with clinical vascular disease. This clinical service subserves four broad areas of patient care

1. Confirmation of diagnosis
2. Prediction of therapeutic result
3. Monitoring of surgical or medical therapy
4. Longitudinal follow up of the natural history or influence of therapy of peripheral vascular disease.

However a direct by product of objective diagnostic information that can be obtained nonobtrusively from the patient is the clinical research that evolves from improved understanding of vascular disease. Thus, much of the recent increase in our understanding of the physiology and clinical aspects of peripheral vascular disease has come from the information obtained in the clinical noninvasive peripheral vascular laboratory

Financial base The noninvasive vascular laboratory should be financially self supporting through the revenues generated by diagnostic services. However this new patient service must not be developed with the objective of income generation but should be efficiently managed to permit fees for services to remain within the limits necessary to support the space personnel, equipment, and operation of the facility The financial operation of the laboratory may be under the auspices of the physician, department or hospital responsible for the laboratory If the facility is operated by the hospital, the fiscal management should take into account the expenses necessary to maintain and develop appropriate equipment, recruit and retain talented technologists, and support the necessary educational activities to permit the facility to achieve its full potential.

Summary

This paper has attempted to provide an overview of the current techniques and operation of the noninvasive peripheral vascular laboratory The past decade has witnessed an increasing interest in noninvasive diagnostic techniques in general and peripheral vascular evaluation in particular There are many instruments which have been developed some of which are inexpensive, simple, and accurate for screening for peripheral arterial, venous, and cerebrovascular disease. The physician must recognize the importance of appropriate selection and interpretation of these diagnostic studies. Specifically the clinician must

place the role of the noninvasive vascular laboratory into proper perspective with that of the conventional diagnostic techniques of history physical examination, and arteriography or phlebography It is anticipated that noninvasive diagnostic techniques will be applied with increasing frequency in the years to come. Only by understanding the principles, applications, attributes, and limitations of the various diagnostic modalities will the clinician be able to intelligently use them in the evaluation and management of patients with vascular disease.

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Tocainide

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Tocainide (Astra Pharmaceutical Products, Inc.) is a new antiarrhythmic drug which chemically is most similar to lidocaine (Fig. 1) Unlike lidocaine, however tocainide is effective when administered orally It has been found to be effective against chronic ventricular arrhythmias associated with a variety of cardiac diseases. Although information is available on clinical use of tocainide, relatively little is known of its effects on experimental arrhythmias. Preliminary data indicate that tocainide, 25 to 200 mg./Kg., administered orally to conscious dogs suppresses ventricular arrhythmias arising after ligation of the left anterior descending coronary artery Similarly intravenous infusion of tocainide, 2 to 25 μg/Kg. completely abolishes ouabain induced ventricular arrhythmias.

The literature on tocainide has been reviewed recently by Zipes and Troup.

1 Clinical use

Tocainide has been used successfully in the treatment of ventricular arrhythmias associated with various cardiac disorders. McDevitt and associates[2] studied the effects of tocainide on ventricular premature depolarizations (VPDs) in eight patients who either had coronary artery disease, mitral valve prolapse or who had no evidence of organic heart disease. All patients had greater than 60 VPDs per hour Five hundred to eight hundred mg. of oral tocainide resulted in a reduction of the frequency of VPDs $\geq$ 60 per cent. Two patients showed less than a 50 per cent reduction in VPDs after maximum doses of tocainide of 800 or 1,200 mg. One patient received only low doses of tocainide 10 to 100 mg. which did not exert an antiarrhythmic effect. These investigators compared the antiarrhythmic effects of oral tocainide to intravenous lidocaine (maximum dose 125 mg. in 30 minute). An equivalent effect of both drugs was observed in two patients, tocainide was more effective than lidocaine in one and less effective in four

Winkle and associates[4] studied the effects of tocainide on the frequency of VPDs in 15 patients. Eleven had coronary artery disease, mitral valve prolapse, or cardiomyopathy four had no apparent organic heart disease. Thirteen patients had all other antiarrhythmic agents stopped at least 5 days prior to study One was continued on propranolol for management of angina pectoris, the other required quinidine for treatment of sustained ventricular tachycardia. An 8 day protocol was used in this study Placebo was administered before and after tocainide, 1,200 to 1,800 mg. per day which was administered on days 2 to 6. The frequency of VPDs before tocainide ranged from 29 to 439 per 15 minute interval. Tocainide caused a greater than 70 per cent reduction in VPD frequency in 11 of 15 patients. Eight showed this degree of suppression at the lower daily dose of tocainide, three showed an equivalent response only at the higher dose. On the last day of study (post tocainide placebo) the frequency of VPDs increased to levels statistically equivalent to pre-tocainide values.

Woosley and co-workers[4] also have studied the antiarrhythmic effects of tocainide in patients with VPDs associated with coronary artery disease and previous myocardial infarction (MI) pulmonary disease, or mild essential hypertension. Two of the 12 patients studied had VPDs of undetermined origin. Tocainide was administered as an initial dose of 400 to 600 mg., a smaller

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have been reported by others,[2-4] with a range of 13 to 22.8 hours and may reflect the effect of cardiac disease on renal excretion of tocainide. Close to 100 per cent of an ingested dose of tocainide is absorbed rapidly from the stomach. McDevitt and associates[4] have pointed out several differences in disposition between lidocaine and tocainide. Lidocaine is removed by hepatic metabolism while tocainide primarily is excreted unchanged in the urine. For lidocaine, 30 to 35 per cent of an orally administered dose may reach the systemic circulation, the majority of the remainder being metabolized rapidly during a "first pass" through the liver. It has been suggested that certain of the lidocaine metabolites may be responsible for the toxicity seen after antiarrhythmic oral doses of lidocaine are administered. For tocainide, within 48 hours after oral administration, approximately 40 per cent of an oral dose can be recovered in the urine; little is cleared in a "first pass" through the liver. Finally, total hepatic blood clearance for lidocaine is approximately 720 mg./minute and for tocainide it is approximately 160 mg./minute.

Plasma protein binding of tocainide is approximately 50 per cent and is similar to that for lidocaine.

Peak plasma levels of tocainide are reached approximately 30 minutes to 4 hours after oral administration. The minimum effective plasma concentration of tocainide ranged from 3.5 to 7.0 µg/ml. with toxicity observed between 10 to 15 µg/ml.

In a study of the clinical efficacy of tocainide in the treatment of ventricular arrhythmias, Winkle and co-workers[3] found that a sigmoid-shaped curve related plasma tocainide levels to per cent reduction in frequency of VPDs. A 70 per cent reduction occurred at plasma concentrations ≥ 6 µg/ml. and a 90 per cent reduction occurred at > 10 µg/ml.

Plasma concentration of tocainide, administered on a 8-hour dosage schedule during a one year study could be maintained between 5.0 to 10.7 µg/ml.

Hemodynamic effects of tocainide

In man, tocainide appears to exert few significant effects on hemodynamic variables. Intravenous doses of tocainide of 7.5 to 11.3 mg./Kg. administered over a 15 minute interval induced slight increases in systolic, diastolic, and mean aortic pressure within 5 minutes. All values returned to control levels within 15 minutes after the end of the infusion. Systemic vascular resistance was slightly increased after 15 minutes of tocainide infusion. Left and right ventricular end-diastolic pressures were increased slightly above predrug levels after 15 minutes of tocainide infusion. Both parameters returned to control values 15 seconds after the end of drug infusion. LV dp/dt was slightly decreased but the change was not statistically significant. Cardiac output, cardiac index, and right atrial pressures were unchanged. Similar effects of tocainide on aortic pressure have been shown by others.

In dogs, large doses of tocainide (120 mg./Kg.) significantly decreased LV dp/dt within one hour after oral administration and reached a maximum at 3 hours of 30 per cent below control values. Aortic flow and mean aortic pressure were decreased slightly or were unchanged. LVEDP was significantly increased to a maximum of approximately 25 per cent above control.[10]

Effects on cardiac conduction

Anderson et al[9] studied 12 patients who did not have overt heart failure or significant valvular disease but who did have coronary artery disease, moderate valvular insufficiency or idiopathic cardiomyopathy. A pre-tocainide electrocardiogram revealed one case each of left anterior hemiblock and left bundle branch block. The remaining 10 patients had electrocardiograms within normal limits. Tocainide, 7.5 to 11.3 mg./Kg. over a 15 minute interval, had only slight effects on cardiac conduction. Heart rate (as determined from R R intervals) remained unchanged or decreased slightly. Sinus node recovery time, expressed as a percentage of spontaneous cycle length, was variably affected by tocainide, increasing in six patients and decreasing in five. Atrial effective refractory period decreased in eight patients, was unchanged in one, and increased in two; the net effect was a statistically significant (17 msec.) increase. The A H interval increased slightly; no AV block occurred at the doses of tocainide studied. Further, no uniform effect of tocainide on the Wenckebach cycle length was observed. A small but statistically significant decrease (22 msec.) in effective refractory period of the AV node was

noted. The A V nodal functional refractory period was unchanged. H V intervals were unchanged by tocainide and QRS duration was similarly unaffected. The right ventricular effective refractory period was decreased by 23 msec. this effect although small, was statistically significant. The rate-corrected QT interval was decreased slightly (11 msec.) by tocainide. Similar lack of effects of tocainide on heart rate, atrioventricular conduction and intraventricular conduction have been reported by others.

In a preliminary communication Gerstenblith and associates reported that tocainide (dose or concentration unspecified) decreased Purkinje fiber action potential duration shifted the membrane responsiveness curve to the right (i.e. depressed action potential upstroke velocity) at any given membrane potential, and induced a slight decrease in resting membrane potential. This effect is not unlike that of lidocaine. In addition, Gerstenblith and associates state that ouabain induced automaticity of isolated Purkinje fibers was abolished by tocainide.

Conclusion

Tocainide is a congener of lidocaine which is effective, both orally and intravenously against ventricular arrhythmias. Its oral effectiveness, relatively long half life and low incidence of serious side effects indicate that it may be a useful antiarrhythmic agent. Further experimentation man and experimental animals thus is warranted to determine the full spectrum of its antiarrhythmic potential and its mechanism of action.

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The pill and circulatory disease

Two large prospective studies in the United Kingdom recently reported that women who had taken the pill were more likely to die from a wide range of circulatory diseases. The larger of the studies, the Oral Contraception Study of the Royal College of General Practitioners (RCGP), has been monitoring the health and oral contraceptive use of approximately 46,000 British women since 1968. In this study the death rate from circulatory disease was five times greater in women who had taken the combined type of pill than in those who had never taken it.

The excess mortality rate from circulatory disease among pill users is not an unexpected finding. It was foreshadowed by earlier case-control studies,[1-4] by analyses of time trends of cardiovascular mortality in young women, and by reports of the physiological and metabolic changes associated with pill use. What is important about the two recent studies is that, because they are prospective in design, many of the criticisms that can be directed to retrospective studies do not apply.

As well as confirming the findings of other researchers, there are several new observations from these studies. The first is that *the pill seems to be associated with an increased risk of* a wide range of circulatory conditions. The excess deaths among the pill takers included conditions such as rheumatic and congenital heart diseases, malignant hypertension, cardiomyopathy, subarachnoid hemorrhage, and mesenteric artery thrombosis—as well as the more familiar conditions such as ischemic heart disease and thromboembolic disease. It is interesting that pulmonary embolism made only a minor contribution to the excess deaths. Of the 33 deaths from circulatory disease in women who had taken the pill, only one was from pulmonary embolism, but 12 were from ischemic *heart disease and 10 were from subarachnoid hemorrhage.*

Also in the RCGP study the duration of pill use was found to affect the risk of circulatory disease: women who had taken the pill continuously for more than 5 years had an age-adjusted death rate from circulatory disease double that of women who had taken it for a shorter period. There was also some evidence—although based on small numbers and therefore tentative—that the excess mortality rate associated with pill use may persist even after it has been discontinued.

The prospective studies provide the first direct measure of the size of the risk associated with pill use. Clearly this is *important for public health considerations. In the RCGP* study women who had used the pill experienced an over-all excess mortality rate from circulatory disease of approximately 1 death per 5,000 pill-users per year. The mortality rate from non-circulatory diseases was similar in both groups. These findings relate predominantly to women taking combined pills which contain 50 μg of estrogen. The excess mortality rate from circulatory diseases was considerably greater than was previously estimated. It was greater than the death rate from accidents in British women of comparable age, and it was greater than the death rate in the study population from complications of pregnancy in those who had never taken the pill. The excess death rate increased with age and with cigarette consumption. Retrospective studies have indicated that hypertension and hypercholesterolemia may also increase the death rate. Unfortunately the role of these factors cannot be assessed from the prospective studies.

One major problem in the interpretation of these findings remains. Women who take the pill differ from those who do not. Had they not taken the pill, would they still have *developed similar circulatory disease? Available evidence indi*cates that they probably would not—but we can only speculate about this.

We do know that pill users are less likely than non-users to have a past history of myocardial infarction, stroke, hypertension, rheumatic or congenital heart disease, diabetes or other vascular disease[5]; they are less obese[6,7] and they take fewer medications. Thus there is no evidence to support the claim that the excess mortality rate among pill users may be accounted for by the pill being selectively prescribed for sick women (as a safer alternative to pregnancy). Indeed the reverse seems to be true. We also know that women who take the pill tend to smoke more than women who do not take the pill. The differences in cigarette consumption are not large, however. The comparisons in the RCGP study adjusted for differences between the two groups in past health, smoking habits, age, parity and social class. The fivefold increase in the mortality rate among pill users was found after these adjustments.

Little is known about the personality or behavioral characteristics of pill users. Still less is known about the effect of personality on circulatory disease risk in women. Nevertheless it seems most improbable that differences in personality could account for the large excess of circulatory disease observed in women who had taken the pill, since the relative risk associated with type A behaviour pattern is reported to be only twofold, compared with the fivefold difference noted with pill use. It has also been suggested that pill users may drink more alcohol than non-users. The association between alcohol consumption and heart disease is unclear but it has been claimed that it may reduce the risk. It therefore seems reasonable to conclude that differences in personality or behavior between pill users and never users would probably have a minor effect on their differential risks of circulatory disease. Moreover it is not clear whether such differences would increase or decrease the risk of circulatory disease in pill takers.

With these recent reports there remains little doubt that the pill has widespread effects on the circulatory system. The consistency of the evidence from a wide variety of sources is most persuasive. In the light of all these findings the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists have suggested to British doctors that renewed caution should prevail when prescribing

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the pill. They suggest that women aged 35 years and older should consider the adoption of an alternative method of contraception, and that women aged 30 to 34 should do so if they smoke or have taken the pill for 5 years or longer.

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Cardiomyopathy and coronary artery disease

The word cardiomyopathy means a pathological state affecting the myocardium. In the affluent western societies by far the commonest basis to pathological changes in the myocardium is coronary artery disease, but this is not described as cardiomyopathy. Neither is this name usually given to myocardial disease due to rheumatism, thyrotoxicosis, congenital lesions, or syphilis. In general, cardiomyopathy implies myocardial disease without known cause. Goodwin and associates[1] (1961) proposed the following definition: A subacute or chronic disorder of heart muscle of unknown or obscure etiology often with associated endocardial, and sometimes with pericardial, involvement, but not atherosclerotic in origin. On the other hand, cardiomyopathy is sometimes employed with a qualifying adjective which does indicate an etiology. Examples are alcoholic, diabetic, nutritional, and infective cardiomyopathy, though the last named is more often described as "myocarditis."

Many patients with coronary artery disease give no history of angina pectoris or of cardiac infarction, have no unequivocal ECG evidence of coronary artery disease, and present with congestive cardiac failure. Such patients are therefore often wrongly thought to have idiopathic cardiomyopathy. Raftery, Banks, and Oram described four patients in which the diagnosis was changed from idiopathic cardiomyopathy to occlusive coronary artery disease after coronary arteriography (which revealed severe obstructive disease) in three patients and after necropsy (which revealed gross cardiomegaly with severe, diffuse atheromatous coronary artery disease) in the fourth.

Because of this diagnostic difficulty, a *Lancet* editorial (1977) suggests that "before congestive cardiomyopathy is diagnosed, coronary artery disease should be excluded." Diagnosis is not an end in itself but a means to helping the patient. Does it matter therefore, if a patient who in fact has coronary artery disease is wrongly thought to have idiopathic cardiomyopathy? By far the most important reason for making an exact diagnosis is that this influences the treatment. Patients with both conditions are given diuretics (in an amount sufficient to keep them edema-free), digitalis (rightly or wrongly), and the same diet and regimen. Patients with idiopathic cardiomyopathy—in common with the victims of other obscure maladies—have been prescribed steroids, but there is no evidence that this is beneficial. When there is obstruction to left ventricular outflow accompanying idio-

pathic cardiomyopathy the operation of resecting the obstructing muscle has been done, with apparent immediat improvement. But this operation can hardly be justified, in view of the bad prognosis and transient benefit. When cardiac failure is due to coronary artery disease, coronary bypass surgery has been attempted, but the results are poor and the mortality rate is high. I practice, therefore, the treatment of congestiv failure due to idiopathic ardiomyopathy is the same as that for congestiv failure due to coronary artery disease.

The obvious means of distinguishing between these tw conditions is coronary arteriography And if this indicates gross occlusion of the coronary arteries there are the strongest grounds for supposing that the basis t the patient heart failure is coronary artery disease. On the ther hand, coronary artery disease is common and it may ell happen that patient appears from the arteriography to ha e degree of this and yet it is not responsible for the cardiac failure, which in fact is due to idiopathic cardiomyopathy

Coronary arteriography is risky especially in the ery sick patients ho are being considered here. It is also expensive. An investigation with these characteristics should only be done t gi the patient unequivocal benefit. I this situation it gives him no benefit and does not al ys even answer the academic question. What is the basis to the cardia failure?

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Of peer review

Since the advent of NIH (National Institutes of Health) and other granting agencies in the medical research field, peer review committees ha been established to evaluate investigators, research laboratories, research plans, and other research activities The term "peer was introduced with good intentions—that is with the idea that those who evaluated the programs ould be peers of the principal investigators. The term peer" means person of the same or equal standing, quality and ability with another But, in spite of good intentions and in the absence of better plan, this review practice has continued ithout continual evaluation It cannot be over-emphasized that those ho review programs assigned to them must be capable and able to appreciate and recognize good research, adequate research facilities and, especially able investigators. Unfortunately this is not what transpires in spite of good intentions.

Those placed on evaluating committees of any sort consider their selection t be an honor The appointment is often listed in the lay press. Indeed, it is an honor to be recognized as one able t review and evaluate the research programs and training activities of *all* investigators, including outstanding ones, assigned to the committee for study But the reviewers are not all peers of the principal investigators, by any means. Good high quality research is produced by very few people—people who devote practically all of their time to their research and who have few if any peers For example, venture research' can be done by extremely few people, and ery few "peers appreciate, accept, or fully understand the importance and special qualities of enture research or those successfully engaged in venture research Therefore, do dedicated capable investigators have peers"? If so, the peers must certainly be few in number And, where are they Who is to find and select them How are they located? And are true peers willing to devote and sacrifice time to serve on such committees, for they are well ware of the difficulties, if not impossibilities, involved in rendering the proper decision for the welfare and advancement of science and research? What bout motivation and dedication of purpose and time? How do peers evaluate these qualities?

The importance of "peer" review decisions and recommendations cannot be over-estimated. Those individuals or groups to whom these decisions and recommendations are referred tend to rely implicitly on these recommendations, so that these recommendations usually become final decisions. What tragedy for science! A system built for error even though structured for fairness and success and good intentions! Too many of the "peers ha the audacity to express opinions and influence final recommendations concerning details of science for which they have had no training and possess practically no knowledge except that which they learned during their review of the respective applications or heard in halls or read casually Too many fail to prepare for their review or even to study in depth the problems prior to the reviewing process. Frequently the program is studied by the reviewers only during the airplane flight to the laboratory to be evaluated. And, many if not most, of the least prepared and least informed "peers express the strongest opinions and greatly influence the final recommendations. There must be better system and one free of politics, emotions, or nepotism. Is the peer review system free of these problems?

Thus, the "peer review system needs careful study Those selected for peer review should be carefully selected and critically interviewed personally and indoctrinated by people who have done and are still engaged in excellent research. There are the doers and the "responders. Both are impor tant, but they play significantly different roles. Surely the peers who judge doers must be doers in the same fields and capable of evaluating the role of the doers. The "peers

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must be true peers—people who are well trained in fundamental research. They must not be data collectors who, after collecting mass of data, merely review it to see what is publishable. They must be capable investigators who know the reliability of methods, apparatus, research plans, and especially the work and capabilities of the investigator whose program is being reviewed. They must be people who would wash their own glassware to make sure it is clean and who participate directly in their own research. They must not be administrators of research, grant managers, committeemen, or conductors ho orchestrate battery of technicians and assistants. How could people evaluate research programs if they ha e never been trained in research, ha never experienced the difficulties in olved, and ha never learned research discipline? And, too few "researchers today hav really been well trained or ha really *learned* the discipline of research. It is not where one has studied that matters, but what one knows and what one can do that is important. Maybe the quality of the research, especially much of the clinical and physiologic research, is so poor that present pee review groups are adequate for such research projects. If tha i so, then what waste of money! This was not true 25 year ago. Review groups then consisted primarily of capable inves tigators actively engaged in fundamental research.

Peers today too often consider themsel es as "police off cers rather than people selected and responsible to hel advance medical science and to help investigators. This i unfortunate for researchers and for science.

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The esophagus and chest pain with normal coronary arteries

There are literally hundreds of cardiac catheterization laboratories in the United States today An increasing number of selectiv coronary cineangiograms are being performed each year in patients with anginal syndromes, and large percentage of these studies ha revealed normal, or near normal, coronary arterial trees. Many hypotheses ha been proposed to explain this phenomenon

In recent years, the importance of esophageal disease with chest pain syndromes has been greatl underestimated. Many investigations of the anginal syndrome ith normal coronary arteries have disregarded the esophagus as possible contributory factor especially when "upper GI series are found to be negativ However in the majority of cases, radiologic examination is of limited value in the diagnosis of esophagitis, since gastroesophageal reflux may be difficult t demonstrate consistently Bombeck and colleagues found that gastroesophageal reflux could be demonstrated by conventional barium meal studies in only 25 per cent of patients.

While the true incidence of esophageal-associated anginal syndromes is unknown, several previous studies serve to estimate the magnitude of the problem. For example, Delmonico and associates studied 117 patients with severe angina pectoris who were found to hav normal coronary arteries. Forty (35 per cent) presented historical evidence of esophagitis; 12 of those were further studied and esophagitis was documented by endoscopy in all patients (radiologic in estigation was largely negativ)

More recently Kemp and co-workers' studied 200 subjects with angina and normal coronary arteries One hundred fifty-five of these had upper gastrointestinal tract (GI) -ray (and cholecystograms). The studies revealed abnormal upper GI x-ray in 28 (and abnormal cholecystograms in 13). These 41 subjects represent 27 per cent of those studied. One onders how many more subjects would ha had esophageal disease diagnosed if additional, more sensitive, esophageal function tests had been performed. Diagnostic studies currently available for the detection of esophageal disorders, including their relative usefulness, ha recently been reviewed.

The most common examples of esophageal disorder that may simulat angina pectoris are reflux esophagitis (with or without hiatus hernia) and diffuse esophageal spasm. That esophageal disorders may be totally indistinguishable from angina pectoris has been reviewed extensi ely in previous studies.

In light of the above, there should now be emphasis on the need for identifying that subgroup of patients with normal coronary arteries who have esophageal disease. By doing so, they can be adequately treated and, when appropriate, excluded from further in estigations attempting to elucidate the pathogenesis of this most peculiar syndrome.

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Letters to the Editor

Provision of carbohydrate in acute MI

To the Editor:

The article by Warren and associates (AM. HEART J. 95:130, 1978) about diet in the Coronary Care Unit, touches on an important practical point. He agrees that there should be no restriction of carbohydrate, because of the possibility that glucose is the beneficial fuel for the acutely ischemic myocardium, but he does not refer to our study[1] showing that provision of carbohydrate in the diet can bring down free fatty acids in patients with acute myocardial infarction. Our more recent work[2] has suggested that such effects of carbohydrate feeding are more likely to be evident in those patients less acutely ill. Whether such reductions of free fatty acid are beneficial to the patient still requires proof, but experimental data suggest that provision of carbohydrate and decreased circulating free fatty acid concentrations should be beneficial rather than harmful.

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Reply

To the Editor:

In his letter Dr. Opie emphasizes two points: the favorable effects of glucose upon acutely ischemic myocardium, and the deleterious influence of free fatty acids—two phenomena which I heartily accept on experimental grounds.

With myocardial cell hypoxia there occurs increased glucose transport into myocardium, increased glycogenolysis, and rapid myocardial glucose depletion as anaerobic heat is produced. The fact that the arteriovenous difference of glucose across ischemic myocardium reportedly is increased while that of free fatty acids is unchanged[2] also suggests preferential utilization of glucose as energy substrate. In the laboratory increased provision of glucose is associated with enhanced myocardial performance during hypoxia. The work of Nixon and colleagues[4,5] suggests further that patients with cardiogenic shock may respond to glucose infusions by increasing cardiac function.

Conversely, free fatty acids in high concentration depress cardiac function in animals, and their levels were shown to correlate positively with arrhythmias and mortality in patients with acute myocardial infarction. Opie and associates[8] have themselves positively related infarct size to peak serum free fatty acid levels in 20 patients with acute myocardial infarction.

A matter of less clarity, however, is the interaction between serum glucose, insulin, free fatty acids, and catecholamines, and its therapeutic implications. Generally, levels of all these substances are elevated in acute myocardial infarction. Patients in shock (precisely those who have the lowest circulating insulin levels),[8] also have increased catecholamine release with presumably secondary increases in free fatty acids. The relative contributions of glucose underutilization, free-fatty-acid myocardial depression, or increased myocardial contractility and work secondary to catecholamine release cannot be judged at present. Thus, exactly how dietary carbohydrate "brings down" fatty acids is not known, but it is possible that increased myocardial performance might improve tissue perfusion, decrease catecholamine levels, and thereby inhibit lipolysis.

Therapeutically, one is left with the options of (1) blocking catecholamine release or action pharmacologically, (2) blocking release of free fatty acids by such agents as nicotinic acid, or (3) supplying ischemic myocardium with a ready source of energy (glucose) which will be preferentially utilized and not depress performance. Until more elaborate maneuvers are proven to be of value, I shall opt for the latter.

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Reliability of CK MB isoenzyme as a predictor of acute MI

To the Editor:

In the April, 1978, issue of this JOURNAL (95:521, 1978), Drs. Roberts and Sobel conclude that CK MB isoenzyme is an absolute indicator of myocardial necrosis, and is particularly useful as an indicator differentiating acute myocardial infarction from myocardial ischemia. However, elevated CK MB has been detected in their work in 16 of 111 patients with unstable angina, characterized by recurring, prolonged episodes of chest pain. They conclude that all of these patients exhibited independent evidence of acute myocardial infarction without any other specifications. In addition, ischemia alone induced by treadmill exercise and documented by ECG in patients with coronary artery disease does not lead to increased plasma MB-CK despite elevated total CK.

In our experience, in 10 patients out of 80 with severe unstable angina documented by ECG, elevated CK MB was found in the presence of normal CPK. We also found in three patients out of 10 with effort angina and positive exercise test, elevated CK MB in the presence of normal CPK. In addition to serial CK MB blood samples that were taken every two hours during the 24 hours after onset of chest pain, simultaneous measurements of serum myoglobin were taken, in order to rule out acute myocardial infarction. The serum myoglobin level was determined by radioimmunoassay method (Myoglobin RIA Nuclear Medicine Systems, Inc., Newport Beach, California, USA). The serum myoglobin is known to be highly sensitive for myocardial necrosis and was not found in myocardial ischemia. The normal serum myoglobin, normal total CPK, and the transient ischemic changes on the ECG ruled out acute myocardial infarction in the presence of significantly elevated CK MB.

These findings strongly suggest that the ischemic but not infarcted cells develop temporary alterations in membrane properties which allow CK MB to leak out. A similar observation was implied in the article by Galen and associates.

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Reply

To the Editor:

Thank you for the opportunity to comment on the above letter and we also thank Drs. Marmor, Keidar, Grenadir and Palant for their interest in our paper. In our review on CK isoenzymes in the April, 1978, issue of the AMERICAN HEART JOURNAL (Vol. 95:521, 1978) we stated that release of MB CK from the heart reflects necrosis rather than ischemia. This statement was based on the following data. MB CK was not released in patients with prolonged episodes of chest pain; exercise-induced cardiac ischemia as detected by ECG was not associated with release of MB CK[1,2] and in the experimental animal occlusion of a coronary artery for less than 20 minutes duration consistently resulted in no release of CK and the heart 48 hours later showed no morphological evidence of necrosis—however, occlusion for 35 minutes or longer consistently resulted in release of CK and morphological evidence of necrosis.

Though this evidence does not prove that release of MB CK from the heart is dependent on cell necrosis, it does provide a framework to interpret the significance of plasma MB CK elevations.

Marmor and colleagues point out the rather interesting finding that in 13 patients they have observed elevated CK MB without an elevation in total CK. Furthermore, the serum myoglobin was also normal. Normal human plasma or serum from 100 normals exhibited MB CK activity ranging from .5 to 5.5 IU/L. Thus, whether one detects MB CK in normal plasma would depend on the sensitivity and precision of the assay. Since the authors do not state either the assay or its sensitivity, it is not possible to discuss the particular attributes with respect to different assays.

However, the authors state that they observed increased MB CK without an increase in total CK. The increased MB CK without an increase in total CK is most likely due to artifact and almost certainly cannot be attributed to either cell ischemia or necrosis. The CK isoenzyme profile of human tissues does not permit an increase in MB CK activity without an increase in total CK activity. The human heart, which is the only rich source of MB CK, has about 85 per cent MM isoenzyme and 15 per cent MB isoenzyme. All other tissues including skeletal muscle have either no MB CK or it is present in only trace amounts. Thus, any increase in MB CK in the plasma would necessitate a much greater increase by severalfold in total CK. Further evidence that the elevated MB CK is artifact is supported by the fact that myoglobin was not elevated. Myoglobin with a molecular weight of 17,000 is a much smaller molecule than that of CK (82,000) and is released more rapidly than that of CK after infarction. Secondly, the heart is rich in both myoglobin and CK, and if in fact ischemia is responsible for release of CK, one should see abundance of myoglobin simultaneously in the blood. The most likely reason for artifact, if one is using electrophoresis to detect the MB CK, is the presence of nonspecific fluorescence

which can be determined by omitting creatine phosphate, the specific substrat for CK, from the reaction medium. If one uses one of the column methods, the most likely explanation would be a carryover of MM into the MB fraction.

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Chronic cardiac denervation infarct size and myocardial blood flow

To the Editor:

I read with interest the study by Dr. Jones and his group (AM. HEART J. 95:738, 1978) which showed that chronic cardiac denervation in the dog resulted in a smaller infarct and smaller area of non-perfused myocardium after coronary ligation.

A likely reason for this is that after coronary occlusion, of small coronary arteries obtains, and prior denervation prevented the development of this spasm. The occurrence of post-occlusion spasm is not in accord with current concepts, as dilation of mural coronary arteries is considered to occur invariably after coronary obstruction. However prevention of post-occlusion spasm provides reasonable explanation for the beneficial effects of cardiac denervation. The spasm would impede collateral flow into the ischemic zone, and its prevention would permit unimpaired flow from adjacent myocardium.

This explanation was offered by Grayson and Lapin[2] in 1966 for the prevention of infarction in the dog by prior procaine anesthesia of the coronary artery and its environs. Blood flow in the myocardium below the ligated and anesthetized artery returned to normal levels by four hours. Adrenergic neuron blockade yielded similar results.

Instead of the proposed spasm developing secondary to coronary ligation *per se* it probably follows ischemic injury of the myocardium (injury-spasm). The severe ischemia of ligation induced an injury reaction in intramyocardial arteries rather than the normal vasodilation. In favor of this, after coronary ligation alone, the level of blood flow continued to fall for several hours, paralleling the development of myocardial necrosis. Also, in reperfusion stud release of the coronary occlusion after two hours did not prevent further reduction in blood flow over the next four hours. It is likely that the "no-reflow" phenomenon of reperfusion studies is due to injury-spasm, and thus is equivalent to post-ligation reduced flow.

Studies showing prevention of post-ligation spasm by interference with the autonomic nervous system are evidence for the importance of neural component of the control of coronary artery blood flow. A dual and cooperating system of coronary blood flow regulation, comprised of the autonomic nervous system and the anoxic feedback mechanism, has been proposed.

Coronary artery spasm usually is related solely to epicardial arteries. However post ligation spasm appears to be intramyocardial, and the occurrence of spasm involving small coronary arteries might have significant implications. For example, if these mural arteries are involved with spasm during the induction and acute course of infarction, and in angina, the importance of collateral channels in protecting against ischemia with attacks of spasm is lessened. Also, the absence of angina with catheter induced spasm might be due to the lack of an intramyocardial component of this spasm.

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Reply

To the Editor:

The comments of Dr. Hellstrom regarding our work on the chronically denervated heart were most sincerely appreciated. In previous publications Dr. Hellstrom has emphasized that neurally mediated vasospasm, such as that known to be involved in Prinzmetal's variant angina, may be operative in limiting collateral flow following acute coronary occlusion and myocardial infarction. Based on the studies cited in the above letter this injury-spasm concept would appear to have substantial merit and presents an attractive explanation for the phenomenon observed by us. Indeed, when it first became apparent that chronic cardiac denervation afforded a protection to the heart after acute coronary occlusion, we were

inclined to attribute the effect to the ablation of sympathetic vasoconstrictor influences. However, when fully evaluating this explanation, it is essential to recognize certain crucial factors which tend to discredit the injury-spasm concept and, thereby its application to our results. Some of the more outstanding of these factors are pointed out below

Of fundamental importance to the injury-spasm hypothesis are the results of Grayson and associates as cited above. These researchers reported that following experimental coronary occlusion, collateral perfusion could be tremendously increased by alpha-adrenergic blockade. However it is well to note that Redding and Rees, in experiments specifically designed to repeat the results of Grayson and co-workers, could not confirm the existence of an important adrenergic influence on the collateral circulation. Likewise, sophisticated studies performed in the laboratory of Dr Scheel have demonstrated that the collateral circulation in the isolated, and thus acutely denervated, canine heart is extremely small. These studies showed that collateral flow following occlusion of either the right, left anterior descending, or circumflex coronary arteries provides only about 20 per cent of the respective resting flow. Furthermore, studies performed by the present author in conjunction with Dr. Scheel showed that collateral flow in the isolated heart is not increased by pharmacological alpha-adrenergic blockade (unpublished observations). Thus, it must be surmised that the coronary collateral circulation normally has very low conductance and is not affected by removal of cardiac nerves.

Finally it must be considered that our own results reported in the paper referred to by Dr. Hellstrom speak against the involvement of an injury-vasospasm mediated by the cardiac nerves. Thus, if the reduction in infarct size observed following coronary occlusion in the chronically denervated heart were due only to abolition of sympathetic vasoconstrictor influences, it would be reasonable to expect a similar reduction in infarct size in the acutely denervated heart with pharmacological alpha-adrenergic blockade. But our results clearly show that the infarct size in the chronically denervated heart was much less, implying that the mechanism involved in the protective effect is more complex than simple removal of vasoconstrictor tone. It appears that the mechanism is of time-dependent nature such that the anti-infarction effect is not fully evident acutely

W have continued to direct our research efforts towards the elucidation of the protective effect of chronic cardiac denervation following coronary occlusion. In recent experiments, radioactive tracer microspheres were used to quantitate left ventricular blood flow before and after acute coronary artery occlusion in nonsympathectomized and chronically sympathectomized dog hearts. Tw important factors were observed. First, the preocclusion blood flow of the chronically sympathectomized left ventricle was found to be substantially less than that of the nonsympathectomized ventricle, even though cardiac work was no different between the two groups. This finding suggests reduced flow demand in the chronically sympathectomized ventricle and agrees with the earlier observation of Gregg and co-workers. Such reduced flow demand may be effective in maintaining the viability of myocardium following coronary occlusion, especially in the peripheral ischemic regions. Second, results demonstrated that perfusion of ischemic myocardium in the chronically sympathectomized heart was tremendously greater than that in the nonsympathectomized control, these quantitative data thereby support the semiquantitative findings reported previously. Thus, it can be seen that both the reduction in flow demand and the increase in perfusion would be expected to lead to the reduction in infarct size observed. However, the precise basis of these changes during prolonged cardiac sympathectomy still remains to be adequately defined.

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Isolated T wave alternans

To the Editor

I read with interest the work of N varro-Lopez and associates in the March, 1978, issue of AMERICAN HEART JOURNAL (95.369, 1978). In Table I the thors list the published cases of T wave electrical alternans. The review is very precise but I would like to add, to make it complete, that I published case of T wave electric alternans in *"Giornale Italiano di Cardiologia* for November-December 1976, page 1120. This work is missing in the review

I agree with Navarro-Lopez and colleagues that T wave alternans occurs when there is severe QT prolongation (which has already been explained by P J. Schwartz and A. Malliani.) However as I explained in my work, I think tw reservations should be made in regard to this statement. the first is that none of the authors has ever seriously attempted to calculate the duration of the T wave correctly carrying out phonocardiographic or pressure recording simultaneously with the ECG the second reservation is that in the published ECG it is almost always impossible to distinguish the P wave from the preceding ST-U tract because—I think—it is the whole terminal complex which presents serious anomalies and not only the duration of Q-T tract.

In addition, I think the statement by Navarro-Lopez and associates that in some case the alternans are associated with hypocalcemia, should be considered carefully because the electrophysiologic action of calcium ion is due to its ionized fraction and to its relation with pH and phosphoremia, and these data have never been checked by any author. Consequently it follows that the report of hypocalcemia associated with T wave alternans could be accidental.

In my work I made an important distinction also. There are

two different types of T wave alternans: "voltage" and "polarity" types. It is difficult to give a similar electrophysiological explanation to these two events unless we appeal to a generical alteration of the calcium ion transportation mechanism at the cellular membrane level.

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Reply

To the Editor:

We would like to thank Dr. Vergassola for his comments concerning our article and for his addition to our bibliography.

In our review we meant to emphasize that the clinical setting of the acquired T wave alternans (TWA) was in some instances very suggestive of its association with hypocalcemia. This was especially clear in Case 2, where TWA was observed for the first time in the absence of pancreatic, renal, or heart disease. We consider Dr. Vergassola's interesting case very similar to our own, further suggesting that these observations may not be so rare as would be expected from the previous literature. We agree with Dr. Vergassola that the pertinent information about the ionized serum calcium level has never been checked in the clinical examples, but we have recently reported on serum electrolytes and blood gas analysis in experimentally induced TWA in dogs by means of calcium-lowering agents, giving additional evidence that the TWA may be the result in some cases of a reduction of the ionized calcium concentration, the total calcium remaining normal or below normal.

Dr. Vergassola appropriately points out the well-known limitations of the QT measurements, although they do not invalidate our conclusions that the QT (or the QU) interval was severely prolonged and the QT alternated. When the T wave overlapped the P wave or the PR segment, an isoelectric PR could be clearly identified every other complex, indicating that the QT alternated. These changes being apparent in different leads make it improbable that they were due solely to the alternant shift of the T wave axis. In view of the QT alternans, we suggested that the TWA could reflect the alternans of the duration of the recovery occurring preferentially in some regions or layers of the heart. These non-homogeneous changes would account for the alternant shift of the T wave axis that is practically constant in the review cases. Further evidence in favor of the suggested electrogenetic mechanisms has been given by one of us, studying the monophasic action potentials of the anterior and posterior epicardial surfaces of the left ventricle in the dog. We do not think that the voltage and the polarity alternans are essentially different types of TWA, since they depend on the degree of the T wave axis shift, that may in turn be related to the importance of the regional differences in the duration of the recovery.

The QT alternans may then be considered a genuine component of the electrocardiographic syndrome consisting of (a) a long QT and a giant T wave, leading to (b) QT and TWA, probably when the QT prolongation and/or the increase in the heart rate shortened the TQ to a critical level, and (c) an increased tendency to ventricular fibrillation of the "torsade de pointe" type. The clinical implication is that in the presence of any of those electrocardiographic signs and clinical setting compatible with a calcium alteration, hypocalcemia should be discarded, even when total calcium concentration is normal, since calcium administration may be the treatment of choice to prevent or avoid recurrence of the ventricular fibrillation.

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Location of valvular involvement in bacterial endocarditis

To the Editor:

The article by McNeill and associates (AM. HEART J. 95:448, 1978) entitled "Bacterial endocarditis. An analysis of factors affecting long-term survival" describing a series of important variables in patients with bacterial endocarditis, warrants some comments. The authors showed a 1-year mortality rate of 56 per cent which, as they commented, was higher than that reported by others. We feel that additional variables like intravenous drug abuse and type of valvular involvement may be operable in affecting prognosis, variables which were absent in their patient population and which therefore influenced their results.

In our institution, we recently followed 19 patients with isolated tricuspid regurgitation for more than one year. All were intravenous drug abusers and for the great majority the infecting organism was *Staphylococcus aureus*. Two patients died within the first 3 months and none during the second year. We strongly believe that patients with bacterial endocarditis involving solely the tricuspid valve have a much better short- and long-term prognosis than patients with involvement of the aortic or mitral valve. This is supported by a previous study from our institution showing a 16 per cent over-all mortality rate for right-sided endocarditis. McNeil and colleagues report includes only one patient with tricuspid

valve involvement, and even this is associated with an aortic valvular lesion. Their patient population does not seem to include patients with drug addiction who would have a higher incidence of isolated tricuspid valve endocarditis with relatively better prognosis.

If we are to meaningfully analyze and compare the factors of high or low mortality for the immediate or long-term prognosis, then we will have to take into account the location of the valvular involvement and consider this factor in a multivariant analysis. Our comparative long-term survival data between right- and left-sided involvement is in preparation.

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Fever leukocytosis, and sedimentation rate in acute MI

To the Editor:

As an aftermath to reading the article by Lofmark, Nordlander and Orinius (The temperature course in acute myocardial infarction, Am. Heart J 96:153, 1978), it was of interest to review the comments made by past great teachers and masters of clinical cardiology upon fever leukocytosis, and sedimentation rate in patients with an acute myocardial infarction. These simple and often useful measurements are sometimes forgotten amidst the sophistication and complexity of present day coronary care monitoring of arrhythmias and hemodynamic data.

Both Dr Paul Dudley White[1] and Dr Samuel Levine[2] stated that the prognosis is worse in patients with fever that is high at the onset and lasts longer than week. In addition, higher white blood cell count may be associated with more extensive infarct. Dr Levine[2] wrote that "the fever is often overlooked if the temperature is taken by mouth as these patients are in shock and the periphery of the body may be actually cold in the presence of true fever." Dr Charles Friedberg[3] indicated that the temperature must be taken rectally and at regular intervals in order to discover slight temperature elevation, and that the white blood cell count is often more sensitive index of myocardial infarction than rise in temperature and may appear before fever is seen. He found no correlation between the degree to which the sedimentation rate increases and the severity or prognosis of the infarction.

The authors of the present article also noted, as judged from elevated SGOT levels, that a fever of longer duration is associated with more extensive infarction. It would be informative to know whether any relationship was observed between the peak temperature elevation and/or the duration of the fever and (1) any increase in the sedimentation rate and white blood cell count, (2) an early pericardial friction rub as distinct from the friction rub of the post-myocardial infarction syndrome, (3) mortality after the first 48 hours, and (4) complications such as shock, congestive failure, and arrhythmias. In addition many physicians, preferring not to disturb patients with myocardial infarction, take oral rather than rectal temperatures. If the authors, perchance, also took oral temperatures, could they comment upon their reliability and upon their correlation with the rectal temperatures in this group of patients.

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Advances in Microcirculation. Edited by B. M. Altura, E. Da is, and H. Harders, Basel, 1977 S. Karger 110 pp. Price $43.0.

This is the seventh olume in this series published on Advances in Microcirculation. The peripheral circulation, and especially the microcirculation is lost sight of in the tremendous excitement expressed today in the heart itself However it is the small blood essels which are concerned directl with deli ering blood to the tissues. These small essels are little discussed in medical education or at meetings oncerned with cardiovascular diseases. Except for blood iscosity and capillary abnormalities in diabetes mellitus, this lume is de oted t discussions of white blood cell rheology and other aspects of the beha ior of the lymphocytes and gra ulocytes in the microcirculation. Although the beha ior of the hite blood cells and platelets ha been observed and reported in many papers on capillaroscopy for many years, this book gathers in this single olume many obser tions for the con enience of the reader Ho the white blood cell beha es in the capillaries and other small vessels of arious tissues is not only extremel interesting and an exciting physiologic phenomenon, but an xtremely important one. The importance is not only related t resistance to infection but also to immune responses and the phenomenon of rejec tion of grafted tissues. This is ery good and somewhat unusual and interesting book. The illustrations are good and the text is well written.

Platelets and Thrombosis. Edited by D. C. B. Mills and F. I. Pareti, London, 1977 Academic Press Inc., Ltd., 190 pages. Price $12.25.

This timely book on Platelets and Thrombosis represents the proceedings of Serono Symposium. The book is concerned with fundamental biologic principles of platelet function, such as its membranes, factor VIII-related proteins, energy metabolism, enzyme activities, thrombus formation, hemostasis, thromboxanes, and related clinical thromboembolic states. This is a good fundamental review of the role of platelets in thrombosis. This book is certainly worth reading but should especially interest hematologists, physiologists, pharmacologists, and those studying thromboembolic phenomena in clinical disease states. It is ery fine review of the present day interest in platelets, an extremely important problem in medicine.

Hypertension. Mechanisms, Diagnosis and Management. Edited by James O. Davis, M.D. John H. Laragh, M.D., and Amy Selwyn, New York, 1977 HP Publishing Co., Inc., 2?? pages. Price $18.95.

Much has been written on hypertension in recent years. There has been an extensive program designed to detect most if not all cases of hypertension in America and to determine its etiology and treat the disease. This book of many contributors is another written on the subject. It is w ll written and well organized. The emphasis on mechanism and the role of renin, angiotensin, and aldosterone will interest students, housestaff, and trainees in internal medicine, nephrology and cardiology. The vascular physiologic and pathologic changes in hypertension should be of interest to trainees. The treatment and approach to diagnosis should interest the physician who manages hypertension. This is a very good book which reviews briefly and ery well most of the aspects of hypertension that would interest the practicing physician. The illustrations are ery good. There is a rather extensive use of color in the illustrations which makes it easy for the reader to appreciate the significance of the figures. This reviewer does not intend to select isolated aspects of disagreement with the contributors. There are some points of difference in interpretation, however. For example, on page 122, the statement is made in the legend of the illustration that in labile hypertension ascular resistance is normal. Arterial resistance must be increased at the time the arterial blood is ele ted. If it is not so, then how is the elevated pressure produced? Furthermore, the same illustration indicated that labile hypertension is borderline. It is not borderline hypertension, it is labile hypertension. Such statements should alert the reader of this book to read it critically and carefully. This book is good addition to the medical literature and the subject is certainly an important one.

Books received

Clinical Pharmacology: Basic Principles in Therapeutics. 2nd edition. Edited by K. L. Melmon and H. F. Morrelli, New York, 1978, Macmillan Publishing Co., Inc., 1146 pages. Price $25.00.

Principles of Cardiovascular Nuclear Medicine. Edited by B. L. Holman, E. H. Sonnenblick, and M. Lesch, New York, 1978, Grune & Stratton, Inc., 246 pages. Price $18.50.

Diagnostic Pointers in Clinical Electrocardiology. By Leo Schamroth, Bowie, Md., 1978, The Charles Press, Publishers, 268 pages.

Sodium and Water Homeostasis. Vol. 1 of Contemporary Issues in Nephrology Series. Edited by B. M. Brenner and J. H. Stein, New York, 1978, Churchill Livingstone, 250 pages. Price $25.00.

The Adrenergic Nerves of the Normal and the Hypertrophied Heart: Biochemical, Histochemical, Electron Microscopic and Morphometric Studies. Vol. 23 of Normal and Pathological Anatomy. By Franz Borchard, Stuttgart, Littleton, Mass., 1978, Georg Thieme Publishers, 80 pages. Price $22.00.

International Congress on Cardiac Ischemia and Arrhythmias

An international congress on cardiac ischemia and arrhythmias will be held in Montreux, Switzerland, on April 1 through 4, 1979. This continuing medical education offering meets the criteria for 18 credit hours in Category I of the Physicians Recognition Award of the American Medical Association. Registration fee for physicians is $225. For further information, contact: Dr. William James, International Medical Education Corporation, 64 Inverness Drive East, Englewood, Colo. 80112.

Refresher course in cardiac imaging

The Sixth Annual Refresher Course in Cardiac Imaging will be offered at the Hyatt on Hilton Head Hotel, Hilton Head Island, S. C., on April 23 through 26, 1979. The course is sponsored by the North American Cardiac Radiology Society. For further information, contact: Larry P. Elliott, M.D., North American Cardiac Radiology Society, University of Alabama in Birmingham, Medical Center, 619 S. Nineteenth St., Birmingham, Ala. 35233.

Health policy and chronic illness: the national debate

A national symposium on health policy and chronic illness will be presented on February 17 and 18, 1979, at the Sheraton-Palace Hotel, San Francisco, California, under the sponsorship of the University of California, San Francisco. CME credit is available. For further information please call (415) 666-2894.

Seminar on bone and chest disease

A seminar entitled "Radiology of bone and chest disease with emphasis on radiologic-pathologic correlation," will be held in San Diego, Calif., on April 23 through 27, 1979, under the sponsorship of the Department of Radiology of the University of California, San Diego, and the Armed Forces Institute of Pathology. Fees for the seminar are $300 for the entire program and $200 for partial enrollment. For registration information, please contact: Mary J. Ryals, Radiology, P.O. Box 2305, La Jolla, Calif. 92038. Telephone (714) 453-7500, ext. 3711.

Sarasota Medical Awards Conference

A conference entitled "The impact of basic research today on clinical medicine tomorrow" will be presented in Sarasota, Fla., on April 26 through 29, 1979. The conference is AMA accredited. For information, contact: Charles R. Estill, President, Sarasota Memorial Hospital Foundation, 1863 Hawthorne St., Sarasota, Fla. 33579.

12th ten-day International Teaching Seminar on Cardiovascular Epidemiology and Prevention

The Council on Epidemiology and Prevention of the International Society and Federation of Cardiology announces its twelfth ten-day International Teaching Seminar on Cardiovascular Epidemiology and Prevention, to be held in Stirling, Scotland, August 26 to September 7, 1979. The Seminar is held in association with the World Health Organization and local hosts. Approximately 30 Fellows can be accepted. Nominees should normally be at the postgraduate level with some residency training or its equivalent, and be interested in cardiovascular disease epidemiology. Partial assistance with travel costs may be available for accepted Fellows. Room and board are provided without cost. *Fluency in English is an absolute essential.* Applications, including (1) a letter of nomination by chief of department or institution, (2) a personal letter of application from the nominee, and (3) the applicant's curriculum vitae, should be received before April 1, 1979 by: Jeremiah Stamler, M.D., Council on Epidemiology and Prevention, International Society and Federation of Cardiology, 303 East Chicago Avenue, Room 1-615, Chicago, Ill. 60611.

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Editorial

Mitral valve prolapse: the specific billowing mitral leaflet syndrome or an insignificant non-ejection systolic click

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In 1975 we endeavored to clarify aspects of mitral valve prolapse (MVP) and to discuss problems and unanswered questions relating to this common but somewhat ill-defined entity. Since that time there have been a plethora of papers relating to the subject, aptly called an "information explosion" by Devereux and colleagues. These have included studies providing data on clinical, echocardiographic and cineangiographic features, the prevalence, underlying pathology and associated conditions, the complications, prognosis and other aspects. In addition, attempts have been made to correlate the accumulated data and to place various manifestations of MVP in perspective. It is important now to assess which questions have been answered and what problems have not been solved. Although there remain many aspects which are not understood or require clarification, perhaps it is most important at this time to suggest how the individual patient or subject presenting with one or more features of so-called MVP should be classified, advised, and treated.

Devereux and associates stated that "mitral leaflet prolapse remains the common denominator and the sine qua non for the diagnosis." That may be true, but when or how do we diagnose MVP as an *abnormal* entity? Both in symptomatic and asymptomatic subjects, MVP has been detected cineangiocardiographically or echocardiographically in the absence of auscultatory features or other manifestations. Conversely, and far more commonly in our experience, we have detected definite, albeit sometimes soft, non-ejection systolic clicks in subjects, again either symptomatic or asymptomatic and with or without electrocardiographic changes, in whom we have been unable to demonstrate echocardiographic or cineangiocardiographic confirmation of MVP.

In our view it is mandatory to identify the specific syndrome, which we have previously called the "billowing mitral leaflet syndrome" (BMLS) and to distinguish this primary or idiopathic MVP from that secondary to pathological processes. Unlike previously, however, in this editorial the term BMLS will be confined to situations in which *symptoms* are associated with features of primary MVP. The BMLS occurs in both sexes and can probably manifest at virtually all ages. It is most common in young and middle-aged females and sometimes has a familial incidence. The BMLS is almost certainly due to a primary leaflet or chordal abnormality with, in some instances, and especially when the degree of MVP is severe, second-

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ary myocardial distortion " or mild dysfunction.[29] Possibly the syndrome is currently being overdiagnosed but patients with symptoms such as palpitations, chest pain, syncope or breathlessness so frequently have the typical auscultatory and other features that its existence and importance must remain undisputed. The BMLS is most commonly encountered by us in patients referred because of symptoms in whom a non ejection systolic click, with or without a non pansystolic (early or late) murmur of mild mitral regurgitation, is detected on auscultation. MVP may or may not be confirmed echocardiographically or cineangiocardiographically and the electrocardiogram can be normal or abnormal.

A problem relating to both diagnosis and management arises when similar auscultatory features are detected in asymptomatic subjects referred either for an assessment of the auscultatory signs or because of T wave changes on the electrocardiogram—in either instance usually detected at a routine or life insurance examination. Relevant to these asymptomatic subjects is the surprisingly high prevalence of auscultatory or echocardiographic features of MVP which has been found in recent surveys of "normal" population groups. These have ranged from 6.3 per cent to nearly 18 per cent.[32] We have encountered an analogous situation on routine examination of electrocardiograms of healthy young women who are prospective employees, as air hostesses, of South African Airways. A number of these girls have had ST segment and T wave changes, compatible with the BMLS, and have then been examined by one of us (J.B.B.) Auscultation may or may not reveal the presence of a non-ejection systolic click and, less frequently an associated non pansystolic murmur It is, regrettably not understood by us why a relatively large number of asymptomatic subjects have auscultatory echocardiographic, and even electrocardiographic features of MVP identical to symptomatic patients referred for assessment and treatment and in whom we make a diagnosis of the BMLS It appears to us, however that it has now become essential for the symptomatic and asymptomatic groups to be differentiated. It has recently been stated by Motulsky [33] and in our view probably correctly that "for every patient with symptomatic mitral valve prolapse , there are hundreds of asymptomatic persons." We shall later discuss some differences in our suggested management of the BMLS patients from that of subjects with identical features of primary MVP except that they are asymptomatic.

In general, like Cobbs,[17] we have found that subjects with isolated systolic clicks are often asymptomatic and that electrocardiographic abnormalities are less common, whereas those with clicks and constant late systolic murmurs are more likely to have symptoms, ST segment and T wave abnormalities and arrhythmias. Symptoms and electrocardiographic changes may be related to the extent of the mitral billow and hence the tug on the papillary muscle, but patients with marked prolapse are not necessarily symptomatic and, conversely mild MVP may be associated with numerous symptoms. A late systolic murmur which starts shortly after the first heart sound or which becomes pansystolic on standing or after amyl nitrite inhalation is indicative of more severe MVP Both procedures reduce the size of the left ventricular cavity so that the mitral leaflets become relatively more redundant with consequent increase in the degree of prolapse.

The large number of patients with the BMLS who suffer from anxiety is noteworthy and is not always understood. In some, anxiety supervenes after an incorrect diagnosis of occlusive coronary artery disease has been made.[19] In others, anxiety in a genuinely symptomatic patient with the BMLS may be caused or aggravated by the insistence of medical attendants that there is no organic heart disease present. It is not "reassuring" to patients with disturbing symptoms, such as chest pain or palpitations, to be told that they are "neurotic." We postulated, as later did Wooley that many cases of so-called DaCosta's syndrome or neurocirculatory asthenia are examples of the BMLS.

It is important, but sometimes difficult, to distinguish the BMLS and so-called primary or idiopathic MVP from secondary MVP The numerous conditions which cause or are associated with MVP are reflected in Table I and we have attempted to differentiate the conditions which are probably causally related as opposed to those which may be chance associations. Inevitably there will often be an overlap and some entities, most importantly myocardial ischemia, rheumatic valvulitis, cardiomyopathy and viral myocarditis may sometimes cause MVP and sometimes be a chance association with primary

Table I Documented conditions causing or associated with MVP or NESC/MISM

Definite or probable cause	Probable association
Primary MVP (BMLS)	Congenital heart disease (atrial septal defect, ventricular septal defect, patent ductus arteriosus, complete absence left pericardium,† membranous subaortic stenosis,† Ebstein anomaly,† corrected transposition of great vessels†)
Marfan syndrome	Athlete's heart
Floppy valve syndrome	Turner syndrome†
Rheumatic endocarditis	*Noonan's syndrome*†
Occlusive coronary artery disease	Congenital prolonged Q-T syndrome†
Congestive cardiomyopathy	
Idiopathic hypertrophic subaortic stenosis	
Myocarditis	
Mitral valve surgery	
Trauma	
Left atrial myxoma	
Polyarteritis nodosa	
Left ventricular aneurysm	
Ehlers-Danlos syndrome†	
Relapsing polychondritis†	
Lupus erythematosus†	
Muscular dystrophy†	
Wolff-Parkinson-White syndrome†	

Abbreviations not in text: NESC = non-ejection systolic click; MISM = mitral incompetent systolic murmur.
†References are given only for conditions which were not mentioned by Barlow and Pocock.

MVP. It may be impossible to detect at a single examination which underlying pathological factor is relevant. There must necessarily be a few patients in whom a diagnosis of asymptomatic primary MVP or of the BMLS is made but in whom the auscultatory and other features are due to the floppy valve syndrome (with or without skeletal manifestations of the Marfan syndrome in relatives), rheumatic valvular disease, or papillary muscle dysfunction. The papillary muscle dysfunction in turn may have resulted from past acute viral myocarditis or reflect an early manifestation of occlusive coronary artery disease or cardiomyopathy. The BMLS is probably a cause of conduction defects as well as supraventricular and ventricular arrhythmias, but the pathogenesis of these is not understood and again a chance association must sometimes apply. The association of MVP with the Wolff-Parkinson-White syndrome has been emphasized. Is this conduction defect caused by primary MVP, is it a chance association, or does the abnormal activation of ventricular contraction result in MVP? The latter explanation is, in our view, most frequently applicable.

The differentiation of the BMLS from occlusive coronary artery disease (OCAD) and the relationship between OCAD and MVP is of great importance. The differentiation of the BMLS with an abnormal electrocardiogram from MVP due to OCAD is clearly much easier in a 20-year-old woman than it is in a 45-year-old man. Even in the latter instance, however, it is our experience that an accurate history, physical examination, and the post-effort electrocardiogram usually suffice to distinguish the two conditions. The chest pain of the BMLS is often unlike that of angina pectoris in that it is fleeting, left-sided, and has no relation to exercise or emotion. In some instances, however, the description of the pain is identical to that of angina pectoris in that it is central, constricting, and may radiate to the left arm. Despite this similarity, we have observed that the duration as well as the factors affecting the onset and offset of the pain may be unusual for OCAD. The problem of MVP, the BMLS, and OCAD can be considered under the following five subdivisions.

1 MVP resulting from OCAD

Several series of patients with late systolic murmurs or non-ejection clicks have contained a few subjects in whom OCAD has been assumed to be the cause of the auscultatory signs on the basis of papillary muscle dysfunction. These have usually been middle-aged or older men with angina pectoris or previous myocardial infarction, in some of whom significant coronary artery disease has been confirmed arteriographically. A

causal relationship is difficult to establish unless the click or murmur has been observed to develop[23] or more conclusively if the patient had been studied by angiography or echocardiography before the ischemic event.

More recently the prevalence of MVP in patients with OCAD has been investigated [4, 44, 46] and some degree of MVP usually involving the posterior leaflet, has been found in from 19.2 per cent to 60 per cent of cases. Although there have usually been fibrosis of papillary muscle and underlying myocardium at necropsy occasionally there has been no detectable abnormality and a functional disturbance has been postulated The valve leaflets and chordae have been normal. Echocardiography has been positive in only a small proportion of patients with MVP demonstrated angiographically[46] and in very few have there been auscultatory signs.[43, 44] This apparent dissociation of angiographic from clinical and echocardiographic features in patients with MVP secondary to OCAD is difficult to explain and Jeresaty[46] has attributed it to an absence of leaflet or chordal abnormality Although exact figures are not available, a soft non-ejection click has been detected in many patients admitted to our coronary care unit with an acute ischemic event. We think it possible that these sounds could easily be overlooked.

It is our impression, but we have no hard data on this, that patients who develop MVP after acute myocardial infarction more often complain of symptoms like those of the BMLS such as atypical left chest pain and palpitations, than do patients with no definite MVP after acute infarction.

2. Coincidental primary MVP (or the BMLS) and OCAD

Both OCAD and primary MVP are common and there has to be a number of patients with both conditions. [46] The electrocardiogram at rest or after effort, is usually abnormal and changes more suggestive of OCAD or of the BMLS may predominate. Where selective coronary arteriography confirms the OCAD and left ventriculography shows relatively mild MVP it is difficult or impossible to be certain whether the MVP is primary or due to the OCAD Where the degree of MVP is marked, we favor the conclusion that the two conditions are occurring coincidentally

3 Primary MVP (or the BMLS) with an electrocardiogram atypical for OCAD

This group includes non-specific T wave changes, the ST segment, and T wave changes described in the BMLS and the abnormal electrocardiograms recorded in some athletes. The T wave changes normalize immediately after effort in the majority of patients. Where the electrocardiogram becomes more abnormal in the post exercise recordings the changes are atypical for myocardial ischemia. Selective coronary arteriography is normal.

4 Primary MVP (or the BMLS) with an electrocardiogram indistinguishable from OCAD

So-called "false-positive post-effort electrocardiograms are reputedly more common in females.[38] In either sex, however a middle-aged patient with auscultatory and other features of MVP chest pain suggestive of angina pectoris, and more than 1 mm. horizontal or down-sloping ST segment depression occurring after effort and lasting for several minutes, may indeed cause difficulty in diagnosis.[1, 4, 39] Engel and co-workers[4] reported such abnormal repolarization responses to treadmill exercise testing in seven of 23 male aircrew members with MVP and normal coronary arteries. Six of the seven were asymptomatic. Malcolm and Ahuja[47] studied 38 patients with MVP by electrocardiographically monitored submaximal exercise stress testing and concluded that the response differed from that considered typical of ischemia, mainly in that the ST segment abnormalities developed immediately after effort and were short lived or alternatively occurred only at 8 minutes or even later None the less, we have encountered a few patients in whom we had no means of distinguishing with certainty the BMLS from OCAD other than by selective coronary arteriography (Fig. 1). It is in this group that thallium 201 myocardial scintigraphy may prove contributory in excluding regional myocardial ischemia and thus make the presence of significant OCAD unlikely [48, 49] This technique has been said[48] to be more accurate than exercise electrocardiography in identifying large vessel ischemia. However there have been recent reports[41] of the patterns of regional myocardial ischemia in patients with MVP and normal coronary arteries and greater experience is needed in interpretation of this relatively new investigation in cases of MVP The possibility of

myocardial ischemia is not excluded by a negative exercise perfusion scintigram nor by anatomically normal coronary arteries but the patient should then be considered under subdivision 5.

5 Primary MVP (or the BMLS) myocardial ischemia or infarction and normal coronary arteriography

The entity of myocardial ischemia or infarction with anatomically normal coronary arteries is now generally accepted. Several investigators favor the conclusion that coronary artery spasm causes the ischemia or infarction but the reason for such spasm is unknown. Chesler and co-workers reported four patients with MVP acute myocardial infarction, and normal coronary arteriograms and postulated that there may be an association between the BMLS and coronary artery spasm. Cerebral ischemic events, attributed to bland emboli, have been reported in cases of MVP and it is possible that small coronary artery emboli provoked spasm in Chesler's cases. If this is true, a therapeutic trial of dipyridamole (Persantin) and salicylates may be indicated in similar cases. The association between MVP and coronary spasm with anatomically normal vessels was observed in one patient by Awdeh and Gholston. More recently Buda and co-workers confirmed an association between coronary artery spasm and MVP. Nine of their 10 patients with coronary artery spasm had MVP.

The possible association between the BMLS and coronary artery spasm requires further observations and study. The mechanism of the chest pain, arrhythmias, electrocardiographic abnormalities, and conduction defects in the BMLS is unknown. Buda and associates postulate that coronary artery spasm may be an important factor and Cobbs has suggested that local coronary spasm might contribute to papillary muscle ischemia.

Cowley and colleagues reported a patient with severe, typical angina pectoris, isolated corrected transposition of the great vessels, normal coronary arteries, and bilateral atrioventricular valve prolapse. The cause of the chest pain in their patient was not understood.

Management and prognosis

The prognosis of a patient with MVP largely depends on whether there is an underlying cause

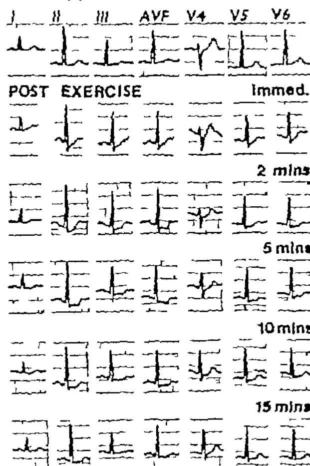


Fig. 1 Pre- and post-exercise electrocardiograms of 35-year-old man with angina-like chest pain and loud non-ejection systolic click. W interpreted the ST and T wave changes, especially in Leads II, III and V at 2 and 5 minutes, as compatible with occlusive coronary artery disease. Selective coronary arteriography was normal.

or associated condition. This is readily apparent when MVP occurs with OCAD or a cardiomyopathy. Conditions such as the Wolff-Parkinson-White syndrome, congenital heart disease, and the congenitally prolonged QT syndrome are as important, or more so than the MVP itself. It is therefore relevant to know of accompanying or causal pathological entities when assessing myocardial function, arrhythmias, conduction defects, or the possibility of sudden death in patients who have MVP. It would not be meaningful, for example, to attribute the cause of sudden death in a patient with triple vessel OCAD to coincidentally associated primary MVP or to MVP secondary to papillary muscle dysfunction. The series of Raizada and asso-

cates[1] indicated, in fact, that MVP is extremely common with triple vessel OCAD

Symptomatic idiopathic or primary MVP—the BMLS. Reassurance as to the generally excellent prognosis for life is essential in the management of these symptomatic and often anxious patients. Symptoms such as palpitations, light headedness, dizziness, or syncope suggest the presence of arrhythmias or conduction defects, but exercise electrocardiography or ambulatory monitoring may be necessary for confirmation. Arrhythmias may occasionally occur without such symptoms and, conversely, dizziness and palpitations have been prominent complaints at times when electrocardiographic monitoring or clinical examination provided no objective explanation. When multifocal premature ventricular contractions, the R on T phenomenon, or ventricular tachycardia are detected, treatment with a beta adrenergic blocking agent is recommended. Other potentially useful therapeutic agents include perhexiline maleate, diphenylhydantoin, disopyramide and mexiletine. In our experience, a good response can be anticipated. There is evidence[11] that the potentially serious arrhythmias are more common if the resting electrocardiogram shows ST segment and T wave changes. Nevertheless, the prognosis, even in this possibly higher risk group, appears to be good and sudden death is extremely rare. Chest pain which may be a disabling symptom, usually also responds well to reassurance and a beta blocker but an occasional patient is encountered who is refractory to both.

Asymptomatic primary MVP. The management of the asymptomatic subject with an isolated non-ejection systolic click, whether loud, soft, or intermittent and in some instances with an associated transient non-pansystolic regurgitant murmur is more controversial. Whether or not echocardiography or cineangiocardiography confirms or demonstrates mild MVP does not contribute to solving the problem of how to assess or treat these asymptomatic subjects, who in recent evidence suggests comprise a large percentage of the apparently healthy population and may represent a "normal" variant. Depending on the context of the situation in which the features of MVP were detected, the person should, in our view, either be assured of the probable insignificance of the [illegible] or not be informed of it at all. An effort electrocardiogram is mandatory only if the individual is employed in an important public service capacity such as an airline pilot, or as part of the assessment for a life insurance policy.

Although asymptomatic subjects may indeed develop arrhythmias after effort, the prognostic significance of this observation remains to be established. It is often customary to perform a stress electrocardiogram on asymptomatic persons with auscultatory features of MVP detected at a routine examination, particularly if the resting electrocardiogram is abnormal. However we have not practiced that policy on schoolchildren or air hostesses detected during surveys. Any patient, including a young woman, who consults a medical practitioner for a "check up" will, in our experience, accept a stress electrocardiogram as part of the examination and that is our usual policy, especially when the resting electrocardiogram is abnormal. An air hostess, on the other hand, singled out from her peers for a stress test, would require an explanation, become anxious, and may even develop a cardiac neurosis. Should, in fact, the post-effort electrocardiogram have revealed ventricular ectopy, is there good evidence and thus sound reason to believe that the girl should be informed, then reassurance attempted and an antiarrhythmic agent prescribed? We contend not!

Progression of mitral regurgitation. Subjects with a *constant* late systolic murmur generally have a less favorable prognosis than do those with an isolated non-ejection click. Echocardiography in this group usually confirms MVP. Although progression of the mitral regurgitation may not occur[13] or is slight and gradual over many years in some, it is difficult to identify the few subjects, usually men, in whom severe mitral regurgitation will supervene. Many of the cases which progress to more severe mitral regurgitation may belong to the much rarer category of floppy valve syndrome. As has already been intimated, we know of no way of recognizing these in the early stage of MVP unless there are skeletal manifestations of the Marfan syndrome in the patient or in relatives. Although we favor that the term BMLS be confined to symptomatic patients with features of primary MVP and that asymptomatic subjects with a non-ejection click, even if accompanied by a transient non-pansystolic murmur, be regarded as "normal variants" who seldom require specific treatment or future

observation, the asymptomatic individual with established, albeit mild, mitral regurgitation due to primary MVP has to become a patient. Periodic, though infrequent, clinical assessment for possible progression of the valve anomaly and advice regarding prophylaxis against infective endocarditis are indicated.

Prophylaxis of infective endocarditis. Infective endocarditis may supervene in MVP and we are well aware[illegible] that occasional cases have been encountered in patients with an isolated non-ejection systolic click. It is now recognized, however, that non-ejection clicks with or without transient mitral systolic murmurs are extremely common. The number of reported cases of infective endocarditis in MVP is still relatively small and in the majority established mitral regurgitation had previously been detected.[illegible] Our current policy is to recommend prophylactic antibiotics at times of risk only to those patients who have established mitral regurgitation as reflected by a constant early, late, or pansystolic apical murmur. Prophylaxis in the large number of subjects, whether symptomatic or not, whose only auscultatory feature is a non-ejection systolic click is impracticable.[illegible]

Concluding remarks

There remain difficulties in assessing whether reputedly abnormal MVP suspected because of auscultatory, echocardiographic, electrocardiographic, or cineangiocardiographic features, is significant or a normal variant in the individual subject. In our view, the management of so-called primary MVP differs importantly depending on whether or not the person is symptomatic. We have reserved the term BMLS for the symptomatic patient with features of primary MVP. Indisputable MVP may be secondary to, or coincidentally associated with, many pathological conditions which are of far greater relevance in determining the prognosis than is the MVP itself. The specific BMLS, a primary leaflet and chordal anomaly, is an important and common clinical entity in which the degree of MVP may be relatively mild despite disabling symptoms. Asymptomatic primary MVP and the BMLS in turn have to be distinguished, but this is sometimes difficult, from the more rapidly progressive floppy valve syndrome or from the secondary causes of MVP such as OCAD, viral myocarditis, rheumatic endocarditis, and cardiomyopathy. Some of the symptoms of the BMLS result from observed potentially fatal arrhythmias and conduction defects. Notwithstanding, we still conclude from the published data and our own experience that the prognosis for life is excellent. Although we have a number of patients with the BMLS in whose families instances of unexplained sudden death at a young age had occurred, and despite our concern expressed over a decade ago regarding the possibility of fatal arrhythmias supervening during exercise or emotion, we have not yet encountered an indisputable case of sudden death due to the BMLS.

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Clinical communications

Mitral valve echoes in patients with mitral valve prolapse syndrome

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Echocardiography has proved of invaluable assistance in expanding our recognition of patients with the mid-systolic click, late-systolic murmur or mitral valve prolapse syndrome. Recently a patient with this syndrome was studied at this institution and noted to have an additional echocardiographic finding in diastole which closely mimicked prolapsing left atrial myxoma or flail posterior mitral valve leaflet. Neither of these conditions was present by other criteria. Such an unusual echocardiographic pattern is not commonly recognized in mitral valve prolapse and the authors were able to find only one prior reference to its presence in the literature. Information concerning its prevalence and specificity are currently unavailable. We therefore undertook the present survey to describe this disorder and uantitate its occurrence in separate populations f patients with and without mitral valve prolapse. Data in support of a possible mechanism for the presence of this echocardiographic picture are also discussed.

Patient populations and methods

Echocardiograms done at this institution in the past three years were reviewed from a series of 100 patients with the presumptive diagnosis of mitral valve prolapse and from a group of 50 patients without this disorder Twenty three recordings were ultimately judged to be technically unsuited for definitive evaluation and were discarded from analysis. Mitral valve prolapse was determined echocardiographically using the criteria developed by Kerber Dillon Popp, and DeMaria and co-workers buckling in midsystole, pansystolic bowing, or pansystolic collapse of the mitral echoes. Of the 83 patients with satisfactory recordings who met these criteria, 50 were female and 33 were male. Their average age was 35.1 years, with a range from 12 to 73 years. Of the control group of 44 patients without mitral valve prolapse, 21 were female and 23 were male with an average age of 40.8 years (range 14 to 63 years)

Echocardiographic examinations were performed with an Ekoline 20A echograph coupled to a Honeywell model 1856 recorder A 2.25 MHz Aerotech transducer with an outer diameter of 1.25 cm focused at 7.5 cm I.F was used. Technics for performing the echocardiograms were reviewed independently by each investigator Unanimous agreement as to the presence of the diastolic echocardiographic finding was required for inclusion in the study

Correlative clinical information was similarly obtained from all patients. Fifteen patients with mitral valve prolapse also underwent right and left heart catheterization. Methods of angiographic motion analysis were as previously described. Group statistical comparisons were made by Chi square and nonpaired Student's t testing with significance defined as probability values less than five per cent.

Results

Three subgroups of patients were categorized for comparisons. The first group of 44 control patients without mitral valve prolapse diagnosed by echocardiogram had a variety of clinical diag-

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noses. These included both cardiac (coronary artery disease, other chest pain syndromes dysrhythmias, and various heart murmurs compatible in nature with either innocent flow murmurs, aortic stenosis, or atypical forms of mitral regurgitation) and non-cardiac diagnoses (renal failure pulmonary emboli, acute pancreatitis, and fevers of unknown origin). None of these patients demonstrated the pattern of diastolic echoes under discussion. Contrasted with these was a population of 83 patients with the mitral valve prolapse syndrome, 71 of whom did not have the diastolic echocardiographic finding and 12 (14.5 per cent) of whom did ($P < .01$ by Chi-square $2 \times k$ contingency testing as compared to patients without mitral valve prolapse)

Typical features of this finding are shown for two representative patients in Fig. 1 After first angling the transducer to locate the mitral valve apparatus, the ultrasonic beam was directed caudally to optimally transverse the structures of the anterior and posterior mitral valve leaflets. As shown, a series of roughly parallel echo signals were observed beneath the anterior mitral valve leaflet. These were very much akin to those previously reported in pedunculated and prolapsing left atrial myxoma (but without an echo-producing tumor mass in the left atrium) or in flail mitral leaflet (such as occurs either in bacterial endocarditis or chordae rupture secondary to myxomatous degeneration) The latter diagnoses were all excluded by differential features in either the clinical course and/or specific laboratory testings.

From the usual array of symptomatic complaints commonly reported by patients with this syndrome (atypical chest pain, dyspnea, fatigue, palpitations, syncope, and congestive heart failure), no one historical symptom predictably distinguished the group with diastolic echoes from those without. Similar results were obtained from a review of the physical findings (non-ejection clicks, late systolic murmurs, gallop rhythms, râles, peripheral edema, and other chest wall and musculoskeletal abnormalities) The group with diastolic echoes did manifest a slight but significantly higher incidence of electrical events as recorded by routine electrocardiogram or 24-hour Holter monitoring. These included *mild to-moderate* numbers *of* premature atrial contractions ($P < .01$) and self limiting runs of ventricular tachycardias ($P < .005$) There were

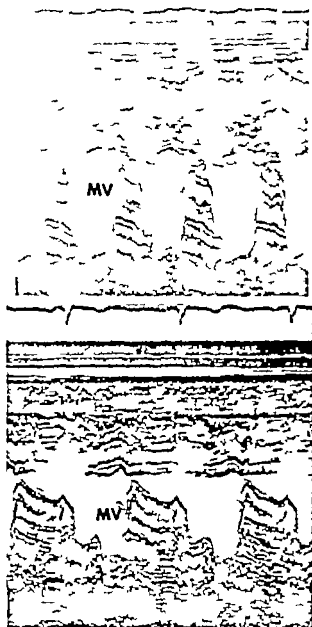


Fig. 1 Two patients *(upper and lower panels)* with representative diastolic echo patterns beneath the anterior leaflets of the mitral valve *(MV)* as observed in their echocardiograms. These findings were typical of those noted in the 12 patients reviewed in this report.

no significant differences in estimates of internal size or geometry for the left atrium, left ventricle and aortic root as measured by echocardiogram.

Fifteen patients with the echocardiographic diagnosis of mitral valve prolapse underwent cardiac catheterization. Four of these patients had the diastolic echo finding under discussion 11 did not. Prolapse of the posterior leaflet of the

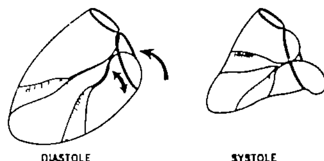


Fig. 2. A schematic illustration (lateral projection) of one possible mechanism to explain the diastolic echoes noted in 12 patients ith mitral valv prolapse discussed in this study. Either through patulous transformation of the leaflet, elongation of the chordae, or loss of support of the inferior papillary muscle, the posterior leaflet during diastole may be drawn forward *(indicated by single rrow)*, possibly from venturi-like effect of rapid ventricular filling, and "curl *(indicated by double arrows)* beneath the anterior leaflet, thus giving rise to the characteristic diastolic echoes.

mitral valve was angiographically confirmed in all cases. There was nothing by hemodynamic status or by contrast angiography to suggest that those patients with the diastolic echoes had more longstanding or severe forms of mitral leaflet prolapse or mitral regurgitation. The group with the diastolic echoes did have postero-inferior hypokinesis beneath the mitral valve as deter mined by segmental motion analysis of the ventriculogram which has been previously reported.

iscussion

A major breakthrough in the diagnosis of mitral valve prolapse has occurred with the advent of echocardiography With proper regard to technique and transducer positioning,[4] this method has provided easily recognizable and highly distinguishing features, the most frequent of which include a smooth pansystolic posterior hammock like bowing of the mitral valve leaflets (perhaps the most common) a mid to-late systolic posterior motion of the leaflets extending at least two mm. posterior from the line of normal coaptation, and/or a marked posterior motion of the anterior mitral leaflet echo back toward the left atrial wall visible for more than 50 per cent of systole. Little has previously been written of any comparable motion abnormalities in diastole Felner and Schlant did report a finding, presumably identical to that described here, which closely mimicked prolapsing left atrial myxoma or valvular vegetations on a flail posterior mitral valve leaflet. They attributed this peculiarity to echoes resulting from hyperdynamic motion of the left atrial wall. Proof of this was not elucidated nor were statistics provided to describe the prevalence and specificity of this pattern in mitral valve prolapse.

Our data, retrospectively reviewed from 83 patients with the click murmur syndrome and from 44 patients without this dysfunction established that the diastolic echoes were unique to those with mitral valve prolapse ($P < .01$). The finding was not common in prolapse patients but did occur with a frequency of 14.6 per cent. None of the many presenting features of the history or physical examination appeared helpful in predicting those patients ultimately found to have the abnormality Similarly there was no evidence to indicate by angiography or echocardiography that the hemodynamic status or mitral regurgitation was worse in those patients with the diastolic echoes. The frequency of dysrhythmias (increased prevalence of premature atrial contractions and self limiting runs of ventricular tachycardia in the subgroup with diastolic echoes) was interesting but too nonspecific for the purpose of identifying subgroups. The differential diagnosis for this finding was confined to alternate considerations of left atrial myxoma and flail mitral leaflet. Myxoma may be easily excluded by additional echocardiographic criteria (no echo-producing mass in the left atrium or echo-free space between the anterior mitral valve leaflet and the diastolic echoes in early diastole) and other clinically distinguishing features. Flail mitral leaflet secondary to chordae rupture may prove more difficult due to the obvious overlap in semantic classifications and clinical spectrums of the two diseases. Chordal dysplasia in the mitral valve prolapse syndrome may lead to spontaneous rupture of one or several chordae, resulting in either no symptoms or variable symptoms. However the classical echocardiographic descriptions of the flail posterior leaflet, with or without valvular vegetations[a] (which could be confused with the present finding) have previously been associated with important destruction of the mitral valve apparatus and consequent hemodynamic collapse.

A recent review of the echocardiographic criteria for determining flail mitral leaflet has been made by Humphries and associates,[13] who proposed four additional findings. In that catego-

ry which could possibly be confused with those of the present study(i.e., flail posterior leaflet), the echocardiograms were not nearly as filled with echo reflecting material as were our cases. Further the clinical presentations again suggested advanced left ventricular failure requiring mitral valve replacement in the majority of patients. Such was not the case in the present study and perhaps serves as the best clue to proper categorization and differentiation. However a mild overlap of patients with myxomatous degeneration of the mitral valve apparatus giving rise to either mitral valve prolapse or asymptomatic chordal rupture still remains.

The mechanism for this diastolic echo pattern is not established. Certain observations in this study suggest that it arises from the posterior mitral leaflet per se. Gilbert and co-workers, employing two-dimensional echocardiography detected in certain patients with angiographically-proven evidence of mitral valve prolapse an unusual and exaggerated excursion of the mitral leaflets during diastolic opening. These motions were observed in a setting of reverse superior displacement of one or both leaflets above the level of the mitral valve ring during systole and were characterized as a rapid and abrupt whip-like opening of the leaflets in diastole. Recent work of DeMaria and colleagues, also using cross-sectional echocardiography showed clear cut morphological abnormalities of the mitral apparatus in the prolapse syndrome including increases in posterior mitral valve leaflet size, width, and length. The angiographic data in one of our patients with the diastolic echoes suggested a unique juxtapositioning of the posterior mitral leaflet with respect to the anterior leaflet during diastolic filling. Taken together these observations provide the basis for detailing one possible mechanism. Either through patulous transformation of the leaflet, elongation of the chordae, or loss of support of the inferior papillary muscle, the posterior leaflet during diastole may be drawn forward and anteriorly possibly from a venturi-like effect of rapid ventricular filling, and curl beneath the anterior leaflet, thus giving rise to the characteristic diastolic echoes. This is illustrated in Fig. 2.

Summary

Echocardiology is an important tool in diagnosing patients with the mitral valve prolapse (MVP) syndrome. An unusual echocardiographic finding reported in this study was observed in 12 of 83 patients (14.5 per cent) with MVP syndrome. The finding consisted of a pattern of multiple, high intensity parallel echoes behind the anterior mitral leaflet noted throughout diastole which in character were closely akin to those previously observed in left atrial myxoma or hemodynamically significant flail mitral valve leaflet. These latter diagnoses were excluded by other criteria. The prevalence of this finding in patients with MVP was significantly increased ($P < .01$ by Chi square contingency testing) when contrasted with 44 patients without MVP. There was no identifying feature in the clinical history or physical examination which could be used to predict those in whom the diastolic echoes were observed. However a significant increase in dysrhythmias as recorded by routine electrocardiogram or 24-hour Holter monitoring was noted. Angiographic information obtained in selected patients suggested that the posterior leaflet per se caused these diastolic echoes. Because of patulous transformation of the valve, elongation of the chordae, or loss of support of the papillary muscle from the posterior free wall, the posterior leaflet appeared drawn forward toward the anterior leaflet, perhaps from a venturi like effect caused by the rapid ingress of blood during diastolic filling. This malpositioning of the posterior leaflet was not associated with significant mitral regurgitation and appears to represent but another facet in the spectrum of mitral valve prolapse.

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The risk of diagnostic cardiovascular catheterization

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In their introduction to the report on the Cooperative Study on Cardiac Catheterization published in 1968, the members of the Steering Committee wrote, "The decision to perform any diagnostic procedure should be based upon the physician's weighing of the *relative benefits* likely to accrue from the resulting information, as opposed to the *potential hazards* involved. While it is not too difficult to assess the potential value to an individual patient of the data obtained by means of cardiac catheterization and angiocardiography it has been far more difficult to estimate the risks to which the patient is exposed. In order to carry out the Cooperative Study sixteen laboratories were selected and the results were pooled and analyzed. These laboratories were well-established facilities in large, mostly university medical centers. The report stated further that, "The Committee appreciated that the results of the study would be affected materially by the identity of the participating laboratories," and the Committee made their selections, " with the recognition that the results of the investigation would be relevant primarily to these and similar laboratories."

It is well known that a host of patients have cardiovascular studies performed in laboratories throughout the United States which may differ in important ways from the type chosen for the Cooperative Study The value of comparing the results from other laboratories with those reported in the Cooperative Study is thus apparent.

In 1965 we established a diagnostic cardiac catheterization laboratory in a private, community hospital associated with a university Prior to its opening, a prospective on going study was planned to evaluate the function of the laboratory and to assess the risk to which the patient was exposed when catheterization procedures were performed. The purpose of this paper is to report our experience with the risk of complications associated with 2,676 various diagnostic catheterization procedures performed in 745 adult patients.

Materials and methods

All catheterized patients were from among those referred to us for cardiac consultation. After taking the history performing the physical examination, and evaluating the laboratory and radiographic information which had been obtained, the senior author recommended cardiac catheterization to those patients for whom it was deemed indicated. All catheterization procedures were either done by him or under his personal, close supervision. Patients routinely remained in the hospital for at least 24 hours after catheterization, and before discharge each was examined by us. Attention was particularly paid to all catheterization sites.

The patients ranged in age from the teens to 83 years of age. The one exception was an eleven year-old patient who was large for his age. Our laboratory was not directed toward pediatric

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Table I Major complications in 745 patients undergoing cardiac catheterization

Complication	Number
Death	0
Serious arrhythmia	2
Profound hypotension	0
Complications involving the arterial system	1
Accidental perforation of the heart	0
Catheter problems	1
Serious infections	0
Serious allergic reactions	0
Embolism	3
Cardiac complications	0
Serious bleeding	0
Pneumothorax	0
Other	0
	Total 7

cases. The percentage distribution of the patients by age beginning with the second through the ninth decade was as follows 9 12, 12 18, 26 22, 0.8, and 0.03 per cent. Using the New York Heart Association functional classification 30 per cent of our patients were Class I 10 per cent were Class II 40 per cent were Class III and 20 per cent were Class IV

For the purposes of this report, patients having electrophysiologic studies or pacemaker electrode insertion were excluded. In our hospital coronary rt ography was a separate procedure done pendently in the radiology department and was not included in this study With these exceptions this series is consecutive and complete. No patient was referred to another institution for additional or supplementary cardiac catheterization When surgery was recommended the patient was referred to one of our hospital s two open heart surgical teams.

Routine premedication usually consisted of 50 mg. of secobarbital and 50 mg of meperidine, which the patient took by mouth one hour before being sent to the laboratory Prophylactic antibiotics and antiarrhythmic drugs were not given The only anesthetic used was a local anesthetic infiltrated at the catheterization site Throughout the procedures all catheters in use were flushed with heparinized saline (4 000 units aqueous heparin per liter of normal saline) Indwelling systemic arterial and venous needles were commonly inserted but produced no complications and their use was not tabulated for this study

Access to the right side of the heart as usually

Table II Etiology of cardiac disease in 74 patients undergoing cardiac catheterization

Etiological group	Patients	
	Number	Per cent
No organic cardiac disease	62	8
Congenital	199	27
Rheumatic	264	35
Arteriosclerotic	43	6
Other acquired	98	13
Mixed or indeterminate	79	11
	745	100

via an antecubital vein. Percutaneous entry of the catheter was preferred, but when a suitable vein was not present an antecubital vein was isolated by cutdown. Systemic arterial blood was sampled from either the brachial, radial, or femoral artery by means of an indwelling plastic needle. Systemic arterial catheterization was always done percutaneously using the Seldinger technic. The femoral artery was preferred, but, at times, it was necessary to use the brachial or axillary artery Whenever a systemic arterial catheter was removed, continuous manual compression of the artery at the puncture site was always applied for at least ten full minutes.

The patients suffered little, if any distress during the procedures which were essentially pain free. Most patients felt that their greatest discomfort was associated with the injection of the radiographic contrast medium

During the catheterizations the usual commonly done studies were carried out, such as pressure recordings, blood sampling for oximetry indicator dilution studies, measurement of oxygen consumption, supine leg exercise, and angiocardiography Special tests were also done at various times.

Our preferred practice was to catheterize the left ventricle in the retrograde direction, including patients with aortic valvular stenosis. In one patient a transseptal (Brockenbrough) catheterization was done

We expected the cardiac catheterization to be completed in from one to three hours. Rarely did a catheterization require more than three hours.

Results

During the 131 months after our laboratory was opened 745 patients underwent diagnostic cardiac catheterization. Table I lists the major

complications observed in these patients. There were no deaths during catheterization and none later which could be causally related to the investigation. In order to facilitate the comparison of the results of this study with the results of the Cooperative Study, Tables I to V were patterned after those in that report.

Table II shows the etiology of the cardiac disease. The most common etiology was rheumatic (35 per cent) closely followed by congenital (27 per cent). The "no organic cardiac disease" group included patients with symptoms possibly related to the heart and those with functional murmurs.

The anatomical diagnoses are presented in Table III. The aortic and mitral valves were, by far, the structures most often involved. In order of decreasing frequency, the most common valvular lesions were mitral regurgitation, aortic regurgitation, mitral stenosis, and aortic valvular stenosis.

Table IV lists the frequency with which various anatomical sites in each patient were entered and the frequency of injection of radiographic contrast medium. In three patients a satisfactory pulmonary arterial wedge position could not be obtained. The left atrium was catheterized on nine occasions, once by transseptal puncture and eight times via an atrial septal defect. The left ventricle was also entered by the same routes in these nine patients. In 672 patients the retrograde approach through the aortic valve was used. One hundred eighteen injections of radiographic contrast medium were made into the right side of the heart. There were 571 left ventriculograms and 551 supravalvular aortograms.

In Table V the incidence of major complications is related to the diagnosis. One complication was listed as occurring in "heart disease, incomplete diagnosis," although we strongly suspected that the patient had a congenitally bicuspid aortic valve. While we were attempting to cross the aortic valve in the retrograde direction the patient suddenly complained about his vision. Examination showed impairment of extraocular muscle movement. The study was immediately discontinued and intravenous heparin was given. A neurology consultant agreed that the patient most likely had sustained a cerebral embolus. The patient rapidly improved and within six hours had fully recovered.

Three patients with rheumatic heart disease had complications. In one patient with severe mitral insufficiency the catheter tip split during the power injection for an aortogram resulting in the loss of the obturator. The distal end of the obturator entered the left ventricle and initiated ventricular fibrillation. Normal sinus rhythm was

Table III Anatomical diagnoses in 745 patients undergoing cardiac catheterization

Diagnosis of lesion	*Number of patients*
No anatomical lesion	63
Atrial septal defect, septum secundum or sinus venosus, with or without partial anomalous pulmonary venous drainage	44
A-V canal defects, including ostium primum defects	8
Ventricular septal defect, pulmonary artery pressure less than systemic	14
Ventricular septal defect, pulmonary artery pressure equal to systemic	2
Ventricular septal defect with pulmonic stenosis (valvular and/or subvalvular), clinically acyanotic	3
Ventricular septal defect with pulmonic stenosis (valvular and/or subvalvular) clinically cyanotic (tetralogy of Fallot) including pulmonic atresia with ventricular septal defect	1
Patent ductus arteriosus	5
Ebstein malformation of the tricuspid valve	1
Pulmonic stenosis: valvular, subvalvular, or supravalvular with intact ventricular septum, including pulmonic atresia with intact ventricular septum	13
Truncus arteriosus all types, including aortic septal defect	1
Coarctation of aorta, all types (infantile and adult)	6
Dextroposition, all forms	1
Tricuspid valve disease (other than tricuspid atresia and Ebstein malformation)	16
Pulmonic regurgitation	2
Mitral stenosis	184
Mitral regurgitation	312
Aortic stenosis, valvular	137
Aortic stenosis, subvalvular or supravalvular	41
Aortic regurgitation	283
Arteriosclerotic cardiovascular disease	87
Primary myocardial disease	28
Cor pulmonale	1
Primary pulmonary hypertension (including multiple pulmonary emboli)	28
Pericardial disease (all forms)	8
Tumor of the heart, great vessels, or pericardium (all forms)	5
Complete heart block	1
Postoperative study	29
Heart disease, incompletely diagnosed	4
Heart or other disease, not otherwise specified	38

Table IV Frequency with which various anatomical sites were entered and the frequency of injection of radiographic contrast medium

Site entered	*Number*	*Angiography performed (number)*
Right atrium	764	19
Right ventricle	763	42
Pulmonary artery	763	57
Pulmonary artery wedge	760	0
Left atrium	9	0
Left ventricle	681	571
Thoracic aorta	671	551

immediately restored by the application of one countershock, no further arrhythmia occurred, and the obturator was recovered at the time of open heart surgery. A second patient, diagnosed as having aortic stenosis and insufficiency developed leg symptoms two weeks after catheterization. Examination confirmed the presence of a femoral arterial thrombus at the catheterization site, and a thrombectomy corrected the problem. A third patient, who had mitral stenosis and atrial fibrillation, had a complete cardiac catheterization easily accomplished without difficulties. About eight hours later while in her room the patient complained to the nurse of the sudden onset of visual difficulties. Examination showed diplopia and the neurology consultant postulated the presence of a cerebral embolus.

One patient had the diagnosis of mitral insufficiency caused by prolapse of the posterior leaflet of the mitral valve confirmed by an uneventful catheterization. Twenty four hours later when the patient was packing her suitcase to go home she called the nurse because of the abrupt onset of trouble seeing. The diplopia found on examination was assumed to be due to a cerebral embolus.

A sixteen-year-old patient with primary myocardial disease developed ventricular fibrillation during catheterization of the right ventricle. The arrhythmia was promptly terminated by one countershock and the study was completed without further incident.

Since six of our 745 patients had a complication, in this series the risk of a patient having a major complication was 0.8 per cent. This compares favorably with the risk reported in the Cooperative Study of 3.6 per cent.

Table V Incidence of major complications related to diagnosis

Diagnosis	*Number of patients with major complications*
Heart disease, incompletely diagnosed	1
Rheumatic heart disease	3
Mitral valve prolapse with mitral regurgitation	1
Primary myocardial disease	1

Table VI provides a summary of the major complications according to the type of catheterization procedure performed. Although an anatomical site may have been entered several times during the catheterization, and multiple injections of radiographic contrast medium may have been made in a single site, in this table each procedure was tabulated as a single event for that diagnostic catheterization. For example, no matter how many times it was necessary to enter various sites in the right side of the heart during a study the patient was counted as having one right sided cardiac catheterization. Similarly although more than one left ventriculogram may have been done in an individual, in this table the patient was credited with having only one left ventriculogram. The number of right-sided cardiac catheterizations (764) exceeded the total number of patients in this series (745) because some patients were returned to the laboratory for repeat studies at a later date.

Table VI shows that 672 patients underwent retrograde left-sided cardiac catheterization and that four sustained a major complication. The 764 right-sided cardiac catheterizations were associated with one major complication. Of 551 patients who had retrograde supravalvular aortography one was classified as having two major complications related to the same event. One hundred eighteen patients had right-sided angiocardiograms and 551 had left ventriculograms, all without complications. In sum seven major complications were associated with the total of 2,676 various catheterization procedures, an incidence of 0.3 per cent.

Table VII tabulates the specific types of major complications and those that left the patient with a permanent residual. Of the three instances of cerebrovascular accident one patient recovered

Table VI Summary of major complications related to type of catheterization procedure performed

Type of procedure	*Number of procedures done*	*Major complications observed*	
		Number	*Per cent*
Right-sided cardiac catheterization	764	1	0.1
Retrograde left-sided cardiac catheterization	672	4	0.6
Right-sided angiocardiography	118	0	0
Retrograde left ventriculography	571	0	0
Retrograde supravalvular aortography	551	2	0.4
	Total 2676	Total 7	Per cent of Total 0.3

Table VII Specific types of major complications observed in 2,676 various catheterization procedures

Type of complication	*Number*	*Number of patients with a permanent residual caused by complication*
Cerebrovascular accident	3	2
Cardiac arrest (ventricular fibrillation)	2	0
Equipment failure (lost obturator)	1	0
Femoral thrombosis (requiring thrombectomy	1	0
	7	2

Table VIII Types of minor complications observed in 2,676 various catheterization procedures

Minor complication	*Number*
Minor arrhythmias (transient)	7
Urticaria (mild to moderate)	5
Vasovagal reaction (mild to moderate)	4
Thrombophlebitis (of vein in arm)	2
Inguinal hematoma (requiring no specific treatment)	1
	19

completely and two patients improved, but, nevertheless, showed some remaining impairment. The four other complications which occurred in three patients were correctable. Thus, in this series of 2,676 catheterization procedures the risk of having a major complication resulting in a permanent deficit was 0.07 per cent.

There were a total of 19 minor complications observed, and these are listed in Table VIII. The instance of inguinal hematoma developed in a patient after she had returned home. Her physician kept the patient in bed for several days, and no specific treatment was necessary. Any sequelae that might have developed after the patients were returned to the referring physicians and which were not reported to us would have resulted, of course, in a reduction of the calculated risks.

Discussion

The risk associated with diagnostic cardiac catheterization for our 745 adult patients was very low. There were no deaths during catheterization and none later which were attributable to it. The risk of a patient having a major complication in this series was only 0.8 per cent, compared to the Cooperative Study figure of 3.6 per cent. Our study, however, differed from the Cooperative Study in several ways.

Our laboratory was limited to the study of adults. Excluding patients 14 years and younger from the Cooperative Study data, though, only slightly reduced the calculated risk of 3.4 per cent.

It was stated in the report of the Cooperative Study that the nature of the case material varied greatly between the participating laboratories. This was most evident from the fact that one of the 16 laboratories contributed about 25 per cent of all of the cases and performed 81 per cent of the coronary arteriograms. Considering the etiology of cardiac disease in cases 15 years and older, the incidence of congenital, rheumatic, and arteriosclerotic disease reported in the Cooperative Study was 19, 28, and 23 per cent, respectively. Table II shows that the comparable figures in our study were 27, 35, and 6 per cent. Thus, our series was composed of relatively more congenital and rheumatic cases and fewer arteriosclerotic cases. Our case material, as mentioned above, did not include coronary arteriograms. This difference, plus the heavy concentration of arteriosclerotic cases added by the one laboratory participating in

the Cooperative Study probably account for the variation in the etiologies of cardiac disease between the two studies. Since as shown in Table III our patients displayed an array of adult cardiac pathology ranging from the rare and recondite to the prosaic and patent, our material was considered to have been representative of the types of cardiac disease present in the community.

In regard to the Cooperative Study it is important to note that the numbers of procedures done in their various laboratories over the two year period were widely divergent, ranging from 196 to 3,064 Indeed, more than half of all of their studies were done in only four laboratories. The risk of catheterization in some of the individual laboratories could, accordingly have been considerably less than the average which was reported in the Cooperative Study Furthermore, the inclusion of data on coronary arteriography in that study but not in ours, may have increased the average risk reported in the Cooperative Study

We believed that we enjoyed some advantages in our study We had continuing, close contact with the patients since our responsibility extended before, during, and after the catheterization. Furthermore, the catheterization team was a small and stable unit, and this allowed for fastidious control of all details of the catheterization.

During cardiac catheterization, tests sufficient fully solve the individual patient's diagnostic problem must be carried out, but it is doubtful that additional catheterization procedures that will not result in a benefit to the patient should be permitted. There may be, however certain exceptions, as when a specific investigative protocol has been established, for example. Procedures as a lagniappe, only serving to give the operators practice, should be avoided. Casual procedures invite causal conjunctures. An issue that is currently unclear is the tendency to include coronary arteriography as a standard addition to many cardiac catheterizations. This seems to be particularly problematical because the role of coronary arterial surgery is presently uncertain and controversial.

Several technical points about cardiac catheterization may be mentioned In our laboratory whether or not its power cord was outlet grounded, every piece of electrical equipment making any contact with the patient was connected to a common central ground. It is important that equipment such as catheters, connectors, and needles be in the best of condition frayed worn or questionable items should be discarded. Our laboratory was designed so that the catheterization could be conducted in a strictly sterile field. Only the surgically sterile operator handled the catheter–manifold system and other sterile equipment used during the study

It is essential that catheterization procedures be done as atraumatically and gently as possible. Indwelling needles should be inserted into vessels, especially systemic arteries, in a minimum number of attempts. A simple point commonly overlooked is that a needle or catheter having a dry surface or one coated with dried blood can irritate the intima of the invaded vessel. This may contribute to the possibility of a thrombosis developing in the vessel. We have found it helpful to keep the catheter clean and moist just before and while advancing it through the vessel by wiping the catheter with a sponge soaked in heparinized saline.

The operator should also keep in mind that fibrin tends to form at the tip of an indwelling catheter within a minute or two when flushing is interrupted. At these times it is requisite to aspirate from the catheter and to discard the aspirated material in order to prevent a subsequent embolus. Needless to say care must always be exercised to prevent air from entering the catheter system.

It seems clear that the risk of cardiac catheterization can be reduced to its minimum only by continuous and careful monitoring of the patient and by meticulous attention to technic. These standards must necessarily be relentlessly enforced from the commencement of the study to its completion. In our view this can be accomplished whether or not instruction is being given to young and inexperienced physicians. From time to time we have had house staff members or cardiac fellows work with us in the laboratory We did not believe that the patient ineluctably received an inferior quality of service or faced a greater hazard because of this, since the tyro received constant oversight and pertinent assistance. Indeed, it is difficult to understand how a trainee could otherwise be properly indoctrinated into the art of cardiac catheterization The guideline for the laboratory under every circumstance must ever be to conduct the catheterization as effi

dently as possible with minimum discomfort and risk to the patient.

The Cooperative Study was an important contribution in defining the risk of cardiac catheterization. It would be of interest for more laboratories to also report their data. Our results showed that the risk to our patients of having a major complication when a catheterization procedure was performed was 0.3 per cent, and the risk of having a major complication resulting in a permanent residual was 0.07 per cent. No patient death was associated with cardiac catheterization. We concluded that comprehensive diagnostic cardiac catheterizations can be carried out with very little risk to the patients.

Summary

This report details a prospective study of the risk of diagnostic cardiac catheterizations performed in a private community hospital.

Over the first 131 months of operation of our laboratory 745 adult patients underwent diagnostic cardiac catheterization consisting of 2,676 various catheterization procedures. Six patients experienced seven major complications two of these complications left a permanent deficit. There were no deaths during catheterization and none later which were attributable to it.

The risk to the patient of having a major complication associated with a cardiac catheterization in our series was 0.8 per cent. The risk to the patient of having a major complication when a catheterization procedure was performed was 0.3 per cent. The risk of having a complication resulting in a permanent sequela was 0.07 per cent.

We concluded that diagnostic cardiac catheterization can be accomplished with little risk to the patient, either of death or of other major complication.

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Propranolol withdrawal in angina pectoris
A prospective study

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There is currently widespread concern that abrupt cessation of propranolol therapy may result in serious cardiovascular complications in patients with angina pectoris. This belief was initiated by isolated reports of myocardial infarction following sudden discontinuation of the drug. Subsequently Miller and co-workers[3] documented serious cardiovascular events in six of 20 angina patients who abruptly stopped propranolol as part of a multicenter drug study. Other investigators[4-] have compiled lists of suspected propranolol withdrawal reactions selected from patients undergoing cardiac catheterization or surgery participants in drug trials and routine office or hospital practices.

None of these studies was specifically designed examine the incidence of propranolol withdrawal reactions. Patients with angina pectoris are often unstable and the natural history of coronary artery disease not infrequently leads to myocardial infarction or other complications whether or not beta-blocker therapy is withdrawn. Indeed, one series of 15 propranolol withdrawal reactions included nine individuals who had unstable chest pain immediately before stopping therapy. It is possible that many of the adverse effects reported following propranolol withdrawal are simply fortuitous. This explanation is supported by the recent publication of several retrospective studies[-] which have failed to show an increase in morbid cardiovascular events after abrupt cessation of propranolol in patients undergoing cardiac catheterization.

In view of these conflicting reports, we undertook the following prospective study to define more clearly the incidence and nature of cardiovascular events in the propranolol withdrawal period.

Methods

One hundred consecutive admissions to Sunnybrook Hospital for elective arteriography were entered into the study. All participants were receiving propranolol for angina pectoris at the time of hospitalization. Symptoms of chest pain were classified according to the New York Heart Association criteria and the extent of coronary artery disease was documented at catheterization. All patients had at least one significant lesion (greater than 50 per cent stenosis) of a major vessel (right coronary left anterior descending, or circumflex artery).

Patients with a stable anginal pattern at the time of booking were admitted one day prior to cardiac catheterization and were instructed by letter to abruptly discontinue propranolol the day before admission. Unstable patients were admitted 48 hours before the scheduled catheterization and the drug was stopped abruptly on the morning of admission.

Changes in the frequency or severity of the chest pain and major complications were documented during both the withdrawal period and the week prior to stopping the drug.

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Results

Patient data. The study group consisted of 100 consecutive admissions (98 patients, two catheterized twice) with the following characteristics: mean age 52.3 years (range 29 to 69 years); 83 males; mean daily dose of propranolol 216.1 mg. (range 30 to 640 mg.); and mean duration of therapy 8.2 months (range 1 week to 96 months).

Propranolol was abruptly withdrawn 39.0 hours (range 24 to 144 hours) prior to scheduled coronary arteriography. A number of patients did not follow instructions exactly and thus the withdrawal time was less than the anticipated 48 hours. Propranolol was withheld for at least 36 hours on 88 occasions.

Seventy individuals had marked limitations in exercise capacity and experienced chest pain at rest or on minimal exertion (Table I). Coronary arteriography demonstrated three-vessel disease in 34 cases.

Cardiovascular complications. Ninety patients exhibited no change in cardiovascular status during the period before and after propranolol withdrawal. There were three cases with minor increases in chest pain and two non-transmural myocardial infarctions during both the pre- and post-withdrawal periods.

Pre-withdrawal period. The three minor and two major events all occurred in the 72 hours prior to the expected time of propranolol withdrawal. One patient who had previously experienced Class II symptoms developed pain at rest and was admitted to hospital 2 days before schedule. A second individual with Class III pain had a single episode of prolonged chest pain unrelated to activity. The remaining patient exhibited a worsening of angina decubitus. In each case cardiac enzymes were normal, propranolol was withdrawn as scheduled, and catheterization was uneventful.

A non-transmural myocardial infarction occurred in a 43-year-old man 36 hours prior to a scheduled propranolol withdrawal. The patient had experienced two previous myocardial infarctions and was booked for elective cardiac catheterization because of the recurrence of chest pain. He was initially started on 160 mg. propranolol daily but continued to have angina at rest. The development of chest pain for 90 minutes, 36 hours prior to the expected time of drug withdrawal necessitated admission to hospital and

Table I. Severity of angina pectoris and number of patients with single, double, and triple vessel disease.

	No. of patients
A. Severity of angina pectoris prior to withdrawal of propranolol (NYHA criteria)	
Class II	30
Class III	41
Class IV	29
B. Number of patients with significant (at least 50 per cent) coronary lesions:	
1 vessel	37
2 vessels	29
3 vessels	34

serial cardiac enzymes and electrocardiograms showed an anterolateral subendocardial myocardial infarction.

The second patient who suffered a major event in the pre-withdrawal period was a 56-year-old male with a history of previous myocardial infarction. During the month prior to catheterization he was experiencing Class IV symptoms in spite of 320 mg. of propranolol daily. Six days before cardiac catheterization, the patient was admitted with prolonged pain at rest and electrocardiograms and enzymes were normal. However, 24 hours before propranolol withdrawal his pains returned and a definite non-transmural myocardial infarction was diagnosed.

In both cases of major pre-withdrawal events, coronary arteriography was performed at a later date and significant two-vessel disease was found.

Post-withdrawal period. There were three minor events during the propranolol withdrawal period. One man with Class IV pain had an increase in the severity and duration of his symptoms during the 48 hours he was off the drug. A second patient with prior Class IV angina had 30 minutes of pain at rest 36 hours after his last tablet. Transient T wave inversion was noted in the anterolateral leads but the cardiac enzymes were normal and the electrocardiogram returned to baseline with 24 hours. The remaining individual exhibited a change in symptoms from Class III to Class IV during the post-withdrawal period and suffered no further sequelae. In all three cases, coronary arteriography was performed and the patients tolerated the procedure well.

A major event occurred in a 59-year-old male

who had prolonged periods of chest pain at rest while receiving propranolol 400 mg. daily. Thirty-six hours after cessation of therapy he developed pulmonary edema and subsequent electrocardiograms and cardiac enzymes demonstrated an anterior non transmural myocardial infarction. Cardiac catheterization several weeks later showed significant left main, anterior descending, and circumflex artery disease as well as proximal left main coronary artery spasm.

The second patient with a major complication while off propranolol therapy was a 61 year-old male who was receiving 240 mg. daily for Class IV angina. Forty hours after propranolol withdrawal he developed prolonged chest pain and pulmonary edema. Serial electrocardiograms and enzymes confirmed the presence of an anterior non transmural myocardial infarction. Subsequent arteriography showed extensive three-vessel disease.

Discussion

In this prospective study patients with angina pectoris undergoing coronary arteriography appeared to be at relatively high risk regardless of whether or not propranolol was abruptly discontinued. These findings are in agreement with previous retrospective studies[4-] and raise the possibility that the morbid events reported in other uncontrolled series may have been fortuitous, reflecting the severity of the patients' coronary artery disease and not the adverse effects of a rebound propranolol withdrawal reaction.

In the present study serious complications occurred exclusively in patients with Class IV symptoms, a group most likely to exhibit deterioration even under the protection of beta-adrenoceptor blockade. Withdrawal of propranolol (sudden or gradual) could conceivably result in a loss of therapeutic benefit in these high risk individuals, exposing them to serious cardiovascular complications. It would seem most prudent to avoid discontinuing propranolol whenever possible for fear of exacerbating symptoms and not because of a putative rebound or withdrawal reaction.

A review of propranolol efficacy trials in patients with angina pectoris also suggests that a rebound phenomenon does not occur following sudden cessation of therapy. Morbid events were as frequent after stopping the drug as in the propranolol or placebo treatments periods. The one report which recorded a 30 per cent incidence of cardiovascular complications involved only 20 patients, a small subgroup of a large multicenter trial. In the entire study myocardial infarction occurred in less than 3 per cent of individuals, which is similar to the 2 per cent incidence during the withdrawal period in the present series.

If propranolol withdrawal results in an increase in angina pectoris via a rebound phenomenon, then one might anticipate finding evidence of sympathetic overactivity in the post treatment period. Investigation of this possibility is currently in progress and preliminary results do not support the concept of a rebound increase in sympathetic activity. Pantano and Lee[14] have found no evidence of rebound hyperexcretion of vanillylmandelic acid following abrupt cessation of propranolol in normal subjects. Similarly there was no change in plasma catecholamine levels in six hypertensive patients during the first week after stopping beta blocker therapy. One group[13] has reported normal sensitivity to beta adrenoceptor stimulation during the withdrawal period and others have not found any change in myocardial contractility at this time.

The mean withdrawal period in the present study (39 hours) was adequate for the removal of beta blockade in nearly all individuals. The pharmacologic effects of propranolol on the heart virtually disappear within 24 to 48 hours after stopping the drug. The plasma half life is 3 to 6 hours,[4-] and levels approach zero after 24 to 48 hours.[12-] Similarly propranolol concentrations in atrial muscle are insignificant within 24 to 48 hours after the last dose[13] and the chronotropic response to isoproterenol becomes normal in 6 to 12 hours.

Of the 100 patients scheduled to stop propranolol, two developed a myocardial infarction within 3 days of the withdrawal date. Although the same incidence was found in those patients off therapy it should be noted that the pre- and post withdrawal periods are not identical in all respects and that this is not a randomized group-matched study. Indeed, failure of 12 patients to follow instructions led to an abbreviated withdrawal time of less than 36 hours. The longer observation time before stopping propranolol would tend to increase the chances of a major event occurring, as would the tendency to unre-

stricted activity in some patients. However several features of the post-withdrawal period would tend to offset these factors.

At the time of hospitalization, patients are more likely to be apprehensive and subject to excessive sympathetic stimulation. The knowledge of an impending catheterization would also tend to raise anxiety levels and provoke chest pain. In hospital it is easier to detect changes in the pattern of a patient's angina and significant complications are more likely to be documented. Activity restrictions also may not protect the individual against serious complications. In a previous study 45 patients had propranolol stopped abruptly a mean of 5.4 days before admission and no morbid events were seen. The single complication occurred 3 days after hospitalization, 11 days after drug withdrawal. Admittedly additional complications may have been recorded in the present series had the withdrawal time been continued for 72 hours. However this period was considered to be unnecessarily long in view of the pharmacologic half life of propranolol and the potential risks for untreated patients who may be dependent upon beta blockade to prevent serious cardiovascular sequelae.

Regardless of the differences between the pre- and post withdrawal periods, the striking similarity in the incidence of morbid events in the 100 individuals before and after propranolol withdrawal must raise substantial doubts about the existence of a rebound phenomenon.

In the present series, four of 29 subjects with Class IV symptoms developed myocardial infarction from the time the catheterization was booked until the actual date of the procedure. The single myocardial infarction in an earlier retrospective study[4] also occurred in a patient with Class IV angina. The cumulative findings in these 153 cases suggest that individuals with chest pain at rest are at high risk of suffering a myocardial infarction and should be catheterized on an urgent basis whenever possible. Unnecessary delay especially if propranolol is discontinued, could lead to serious cardiovascular sequelae. Since none of the patients with less severe angina experienced any significant complication, it appears that the majority of individuals with stable angina who are receiving propranolol therapy are not in immediate danger if tablets are missed for short periods of time.

Current prescribing recommendations suggest that the propranolol dosage should be tapered whenever the drug is electively discontinued. There is virtually no evidence to support this practice and no data have been presented comparing the relative benefits of gradual versus abrupt withdrawal. Until this information is available, we believe that propranolol withdrawal should be performed on an individual basis. Patients with pain at rest appear to be at highest risk regardless of whether or not the drug is discontinued, and urgent surgery with the shortest possible withdrawal time is indicated. Alternatively continuation of therapy until the time of operation may be preferable in some cases, particularly if a high degree of beta adrenoceptor blockade is not present. The routine practice of tapering the dosage in all patients may be potentially hazardous by exposing certain individuals to unnecessarily long periods of insufficient beta blockage, during which time serious cardiovascular sequelae may occur.

Summary

In a prospective study 100 consecutive patients (mean age 51.3 years) with angina pectoris had propranolol abruptly discontinued 24 to 144 hours (mean 39.0 hours) prior to elective coronary arteriography. The mean duration of therapy was 8.2 months and the mean daily propranolol dose was 216.1 mg. New York Heart Association Class II, III and IV symptoms were present in 30, 41 and 29 patients and one, two or three coronary arteries were more than 50 per cent narrowed in 37, 29 and 34 cases, respectively.

Three patients experienced minor increases in chest pain and two suffered non transmural myocardial infarctions prior to the time of scheduled cessation of therapy. The same number of minor and major complications occurred in the post withdrawal period. All four patients who developed non transmural myocardial infarction in this study had pre-existing Class IV symptoms. The course of the remaining 90 patients was uneventful. These findings do not support the concept of a rebound propranolol withdrawal reaction.

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Incidence of mitral valve prolapse in subjects with thoracic skeletal abnormalities—A prospective study

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Thoracic skeletal deformities are commonly observed in patients with organic heart disease[1-] and are known to cause pseudo heart disease.[2-] Pectus excavatum is associated with atrial septal defect in Holt Oram Syndrome,[...] and with aortic and mitral valve disease in Marfan's syndrome.[...] A high incidence of straight back deformity has been noted in patients with atrial septal defect. Recent studies[4-] indicate the frequent occurrence of straight back, narrow anteroposterior diameter of the chest, scoliosis, and pectus excavatum in patients with mitral valve prolapse syndrome (MVPS). In view of the increased frequency with which these deformities are associated with MVPS, it has been suggested that skeletal abnormalities be considered non-auscultatory features of MVPS. To date there has been no prospective study regarding the incidence of MVPS in subjects with various thoracic skeletal abnormalities. This investigation was undertaken to define by clinical examination and noninvasive procedures, the frequency of MVPS in such subjects.

Material and methods

Eighty consecutive patients with straight back (loss of normal dorsal kyphosis), pectus excavatum, and clinically obvious shallow chest (asthenic habitus) were selected for the study. Since the diagnosis of thoracic skeletal abnormality was based entirely on the clinical appearance of the bony thorax, the scoliosis patients were not included in the study as it was difficult to appreciate mild scoliosis without radiographic examination. The patients were screened in the electrocardiography laboratory of New York Veterans Administration Hospital where they were referred for routine electrocardiography. Of the 80 patients, 76 were males and four were females. Their ages ranged from 18 to 80 years. A detailed history was obtained with particular emphasis on chest pain, dizziness, palpitation, and exertional dyspnea. An effort was made to characterize chest pain as typical or atypical. Atypical chest pain was defined as chest discomfort unlike angina pectoris in location and quality, poorly related to exertion and unrelieved by rest or nitroglycerin. The physical examination included careful examination of the bony thorax, and detailed examination of the cardiovascular system. Auscultation of the heart was performed in supine, left lateral, sitting, and standing position.

Laboratory investigation of each patient included 12-lead electrocardiogram, posteroanterior and lateral chest x rays, and simultaneous phonocardiogram, apexcardiogram, and indirect carotid pulse tracings recorded on a multichannel photographic recorder (Irex Medical Systems) at a paper speed of 100 mm. per second. The phonocardiographic microphone was placed at the cardiac apex and left second intercostal space. The echocardiograms were recorded with a Smith Kline Ekoline 20A ultrasonoscope utilizing 2.25

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Table I Comparison of AP diameter and AP/TD ratio of Group 1 and 2 with normal subjects

	No. of patients	AP (cm) mean ± SD	AP/TD % mean ± SD
Group 1 (Narrow AP diameter)	34	10.73 ± 0.96	35.31 ± 2.39
Group 2 (Straight back)	13	10.78 ± 0.96	34.68 ± 2.44
Normal	60	14.20 ± 1.69	47.0 ± 5.15
P value			
Group 1 vs Normal		< 0.001	< 0.001
Group 2 vs Normal		< 0.001	< 0.001

Normal standards reported by Twigg and associates.
Abbreviations: AP = anteroposterior diameter of chest; TD = transverse diameter of chest.

MHz transducer of 1.25 cm. diameter focussed at 7.5 cm., with a repitition rate of 1,000 impulses per second. Simultaneous "M" mode echocardiogram and ECG were recorded on a strip chart recorder (Honeywell 1856A visicorder). The records were made at a paper speed of 5 cm. per second. The patients were examined in supine or semi left lateral positions. The transducer was placed on the third, fourth, or fifth interspace close to the sternal edge. Aortic, mitral and whenever possible tricuspid valve echoes were obtained using standard techniques. Care was taken to hold the transducer perpendicular to the chest wall while obtaining mitral valve echoes to avoid false positive mitral valve prolapse which occurs with inferior angulation.

Phonocardiograms and echocardiograms were interpreted independently by two observers (A. S and M. U). The diagnosis of MVPS was based on echocardiographic or phonocardiographic abnormalities using previously published criteria and was made only when both observers agreed

Radiographic examination of chest The standard posteroanterior and lateral chest x ray films were studied for bony deformities Anteroposterior diameter (AP) of the chest was measured along a perpendicular line drawn from the posterior border of sternum to the anterior border of the eighth thoracic vertebra The transthoracic diameter (TD) was measured at the level of the diaphragm. The ratio of AP TD diameters was obtained and expressed as a percentage.

The 80 patients were divided into three groups

Table II Prevalence of mitral valve prolapse in various thoracic skeletal abnormalities

Thoracic abnormality	No. of patients	Positive for MVP	% of total
1. Narrow AP diameter	34	12	35
2. Straight back	13	7	54
3. Pectus excavatum	33	6	18
Total no. of patients	80	25	31

Abbreviations: MVP = mitral valve prolapse; AP = anteroposterior diameter of chest.

on the basis of the predominant skeletal abnormality

Group 1 Shallow chest (Narrow AP diameter 34 patients) All individuals in this group were asthenic. Six of these subjects also had mild pectus excavatum.

Group 2, Straight back (13 patients) These individuals also showed narrow anteroposterior diameter of chest as in Group 1

Group 3, Pectus excavatum (33 patients). These subjects also had varying degrees of thoracic kyphosis in addition to pectus excavatum deformity Two patients in this group also had narow AP diameter of chest.

Student's t test was utilized to compare the radiographic thoracic measurements of Group 1 and 2 patients with normal values reported by Twigg and associates.

Results

The AP diameter and the AP/TD ratio of the chest were significantly lower in Group 1 and Group 2 compared to those reported in normal subjects by Twigg and colleagues ($P < 0.001$) (Table I)

Incidence of mitral valve prolapse Twenty five of the 80 patients (31 per cent) showed evidence of mitral valve prolapse. In 22 patients MVP was diagnosed by echocardiography Of the remaining three patients, two had midsystolic clicks and one had midsystolic click with late systolic murmur In all three the click moved closer to the first heart sound with decrescendo systolic murmur in the standing position. The echocardiogram did not show mitral valve prolapse in these three patients.

The incidence of MVP in the three groups is shown in Table II The highest incidence of MVP



Fig. 1 Lateral and posteroanterior chest x-ray films of patient with straight back.

was found in patients with straight back (54 per cent), followed by patients with shallow chest (35 per cent), and pectus excavatum (18 per cent) A typical example of chest x ray echocardiogram, and phonocardiogram of a patient with straight back is shown in Figs. 1 and 2. Figs. 3 and 4 demonstrate the chest x ray echocardiogram, and phonocardiogram of a patient with severe pectus excavatum deformity Fig. 5 demonstrates echocardiogram and phonocardiogram of a patient with mild pectus excavatum deformity The incidence of MVP did not appear to be related to the degree of pectus excavatum deformity

The clinical and laboratory data of the 25 patients with MVPS were as follows.

Symptoms Three of the 25 patients (12 per cent) were totally asymptomatic, including a patient who had both mitral regurgitation and aortic regurgitation with atrial fibrillation Thirteen of the 25 patients (52 per cent) had chest pain. Eleven patients had atypical chest pain and two had classical angina pectoris. Thirteen patients (52 per cent) had exertional dyspnea, of whom five had clinical evidence of congestive heart failure including two patients with clinical evidence of tricuspid regurgitation. Fifteen patients (60 per cent) complained of dizziness. Eight of these 15 had a normal ECG four had sinus bradycardia, two had atrial fibrillation, and one had Wolff Parkinson White (WPW) syndrome with paroxysmal supraventricular tachycardia. Six patients (24 per cent) had experienced palpitations. One of these six had a normal ECG and one each had sinus bradycardia with sinus arrhythmia, sinus bradycardia with frequent ventricular premature systoles (VPS) WPW syndrome, atrial fibrillation, and normal sinus rhythm with frequent VPS

Phonocardiography Twenty-three of the 25 patients had positive auscultatory and phonocardiographic findings. Nine (36 per cent) had non-ejection systolic click and systolic murmur 12 (48 per cent) had systolic murmur without click, two (8 per cent) had non-ejection click without any murmur and two (8 per cent) had neither click nor murmur even in sitting or standing position. The timing of the systolic click was midsystolic in seven, late systolic in two early systolic in one and one patient had multiple clicks. The timing of the systolic murmur was holosystolic in 11 patients (including one with late systolic accentuation) late systolic in five and early systolic in five. Of the 11 patients with holosystolic murmur 10 had no clicks and one had multiple systolic clicks. In all patients with mid and late systolic clicks, the click moved closer to the first sound in the standing position.

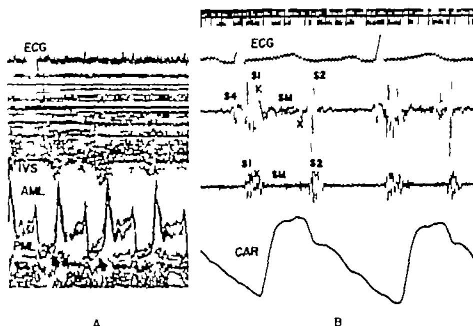


Fig. 2. A and B. *A*. Echocardiogram showing holosystolic prolapse of the mitral valve *(arrow)* in the patient whose chest x-ray is shown in *Fig. 1*. *ECG* = electrocardiogram, *IVS* = interventricular septum. *AML* = anterior leaflet of the mitral valve; PML = posterior leaflet of the mitral valve; *PW* = posterior wall of the left ventricle. *B*, Phonocardiogram of the same patient showing apical holosystolic murmur *(upper phonocardiogram)* with late systolic accentuation and click (x). S_4 = fourth sound, S_1 = first sound, S_2 = second sound; *SM* = systolic murmur; *CAR* = carotid pulse.

Echocardiography. Twenty two patients had echocardiographic evidence of MVP, of whom 11 had holosystolic prolapse of the mitral valve and the remaining 11 had mid late systolic prolapse. In one patient the echocardiogram showed asymmetric septal hypertrophy and systolic anterior motion of the mitral valve without MVP. His phonocardiogram, however, was characteristic of MVP in that it showed a midsystolic click in the supine position which became early systolic followed by decrescendo systolic murmur in the standing position. Two patients also had associated tricuspid valve prolapse. The echocardiogram of the mitral and tricuspid valves, and the phonocardiogram of one of these patients are shown in Fig. 6. Two patients had clinical, phonocardiographic and echocardiographic evidence of associated aortic regurgitation. The timing of the systolic murmur corresponded well with the timing of the mitral valve prolapse on echocardiography in 60 per cent of the patients. Nine of the 11 patients with holosystolic murmur had holosystolic prolapse of the mitral valve and the remaining two had mid late systolic prolapse. In three patients with late systolic murmur the mitral valve prolapse was also late systolic. Of six patients with early systolic murmur five had late systolic prolapse and one had holosystolic prolapse.

Electrocardiogram. The electrocardiogram was normal in 11 patients (44 per cent). Nine (36 per cent) showed sinus bradycardia (including two with sinus arrhythmia). Of the remaining five patients, three had atrial fibrillation, one had wandering atrial pacemaker with A V junctional tachycardia and one had WPW syndrome. Inverted T waves in Leads II, III, aVF, V and V were observed in three patients (12 per cent). Three patients had frequent VPSs (12 per cent).

Discussion

The mitral valve prolapse syndrome has been recognized with increasing frequency since the advent of echocardiography. The sensitivity of echocardiographic diagnosis of mitral valve prolapse is well established by correlation with left ventricular angiographic studies.[u] The diagnosis of MVP in our study was based upon clinical, phonocardiographic,[**] and echocardiographic criteria. However there is no ante-

mortem "gold standard for the diagnosis of MVP as indicated by Markiewicz and colleagues. A high incidence of thoracic skeletal abnormalities in patients with mitral valve prolapse has been reported in retrospective studies.[14] Bontempo and associates[15] reported a 61 per cent incidence of thoracic deformities in 64 patients with MVPS Scoliosis was present in 39 per cent, straight back in 23 per cent, and pectus excavatum in 11 per cent. In 24 patients with MVPS Salomon and co-workers found that 75 per cent had thoracic skeletal abnormalities of which the commonest deformity was pectus excavatum (62 per cent) followed by straight back (17 per cent) and scoliosis (8 per cent) In our prospective study we have found a 31 per cent incidence of MVPS in 60 patients with various thoracic deformities. The prevalence of MVPS in the general population has varied widely depending on the population studied and the method of diagnosing MVPS. Using auscultatory criteria, Barlow and colleagues[20] reported 1.45 per cent incidence of MVPS among black South African schoolchildren. Recent reports, however suggest a higher incidence of MVPS in the general adult population with a relatively greater incidence in females than in males. [21] Markiewicz and associates found a 17 per cent incidence of MVPS in healthy young females. Brown and colleagues found a 6 per cent incidence of MVPS in young healthy females and a 0.5 per cent incidence of MVPS in young healthy males. Thus the 31 per cent incidence of MVPS in patients with thoracic skeletal abnormalities is substantially higher than the incidence in the general population. Such a high incidence is particularly impressive since 95 per cent of our patients were males. The highest incidence of MVPS in our study was in patients with straight back (54 per cent) followed by patients with narrow AP diameter of chest (35 per cent) and least among patients with pectus excavatum (18 per cent)

The reason for the association between thoracic skeletal abnormalities and higher incidence of MVPS is not definitely known. It has been suggested that MVPS, pectus excavatum, and scoliosis are manifestations of forme fruste of Marfan's syndrome.[22] There may be an embryologic explanation for this association since the primordia of the mitral valve undergo differentiation to their final form at the same time that the



Fig. 3. Lateral chest ray film of patient with severe pectus excavatum deformity

vertebral column and the thoracic cage are beginning their chondrification and ossification.[24] A defect in growth patterns at this stage of development might affect both the mitral valve and the bony thorax. Furthermore mitral valve prolapse is known to be associated with connective tissue disorders such as Marfan's syndrome, Ehlers Danlos syndrome,[25] periarteritis nodosa,[25] joint laxity[26] and with congenital lesions such as atrial septal defect,[27] Ebstein's anomaly[28] and Holt Oram syndrome[29] Such an association of MVPS with a variety of connective tissue disorders suggests that MVPS may represent one expression of a systemic connective tissue disorder Hence it is logical to attempt to link thoracic abnormalities and MVPS on the developmental or genetic basis.

Although this study was not primarily designed to evaluate the acoustic characteristics, ECG abnormalities, or association of MVPS with other cardiac lesions, certain interesting observations were made. All patients with a holosystolic murmur except one did not have audible or recordable systolic clicks. Absence of clicks with the holosytolic murmur of MVP has been reported by others. [30] The onset and duration of systolic murmur correlated with the timing of

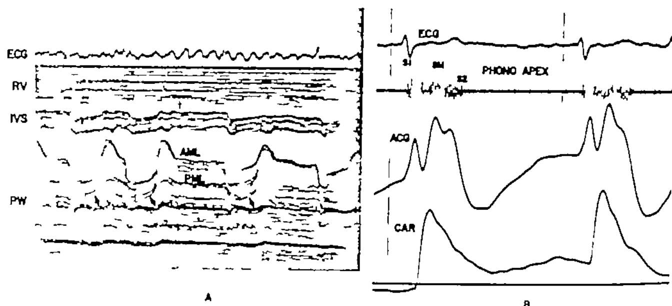


Fig. 4. A and B. *A* Echocardiogram of the patient (whose chest -ray is shown in *Fig 3*) showing holosystolic prolapse of the mitral valve *(arrow)*. *B* Phonocardiogram of the same patient showing mid and late systolic murmur *ACG* = pexcardiogram. Note systolic retraction on ACG at the time of onset of the systolic murmur

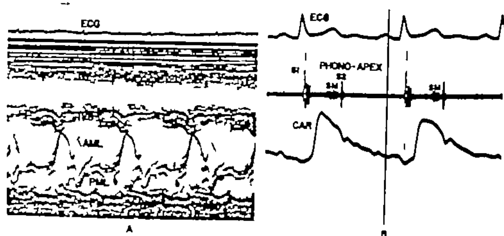


Fig 5 A and B *A* Echocardiogram of patient with mild pectus excavatum showing mid late systolic prolapse of the mitral valve. *B* Phonocardiogram of the same patient showing late systolic murmur

mitral prolapse in 1? patients. Two patients had isolated non-ejection clicks and two patients had the so called silent MVPS Silent MVPS has been reported in 10 per cent of patients with echocardiographic and angiographic evidence of MVP Two patients (8 per cent) had associated tricuspid valve prolapse The incidence of tricuspid valve prolapse in association with MVP is probably higher as reported by others. [8] Two patients had associated aortic regurgitation It has been suggested that aortic valve and aorta are frequently involved in MVPS.[..] Co-existence of idiopathic hypertrophic subaortic stenosis with MVPS is also known.[..] One of our patients had only phonocardiographic evidence of MVP while his echocardiogram showed asymmetric septal hypertrophy with systolic anterior motion of the mitral valve. Electrocardiographic abnormalities are common in patients with MVPS, and these were observed in 56 per cent of our patients. The most common abnormality was sinus bradycardia, which occurred in 36 per cent of the patients.

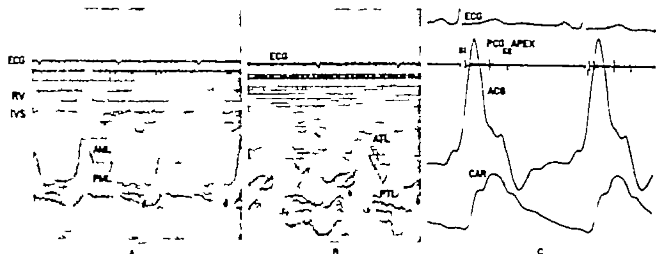


Fig. 6. A through C. Echocardiogram and phonocardiogram of patient with mitral and tricuspid valve prolapse. *A*, Holosystolic prolapse of the mitral valve (*arrow*). *B*, Tricuspid valve prolapse (*arrow*). *ATL* = anterior leaflet of the tricuspid valve; *PTL* = posterior leaflet of the tricuspid valve. *C*, Phonocardiogram showing isolated midsystolic click.

The occurrence and significance of brady arrhythmias in MVPS has been reported previously.[?] T wave inversion in Leads II, III, aVF, V and V_6 was observed in only 12 per cent of our patients. A higher incidence of WPW syndrome, particularly type A, in MVPS has been noted in previous reports.[34] One patient in our study had WPW syndrome type B.

Mitral valve prolapse syndrome is generally thought to be a benign disorder. However serious cardiac complications include life-threatening cardiac arrhythmias,[?] sudden death,[?] [?] infective endocarditis,[?] [?] rupture of chordae tendineae,[?] [?] and progressive mitral regurgitation with congestive heart failure.[?] In the long term retrospective follow up by Mills and colleagues,[?] the complication of endocarditis and progressive mitral regurgitation occurred with higher frequency in those with late systolic murmur than in those with isolated non-ejection clicks alone. Also all complications were more frequent in men than in women in their study. Since MVPS occurs with high frequency in patients with thoracic skeletal abnormalities, these patients are at a risk of developing MVPS related complications. The somatic features of thoracic skeletal abnormalities are easy to identify. A search for MVPS should be made in all such patients, even when asymptomatic, utilizing clinical examination, phonocardiography and echocardiography. Appropriate use of antibiotic prophylaxis against endocarditis, and anti-arrhythmic agents may prevent some of the serious complications of MVPS.

Summary

The incidence of mitral valve prolapse (MVP) in 80 patients with various thoracic skeletal abnormalities (TSA) was examined prospectively using complete history and physical examination, chest x rays, electrocardiography, phonocardiography and echocardiography. There were 6 males and four females, ranging in age from 18 to 80 years. Thirty four patients had narrow antero-posterior diameter of the chest (asthenic habitus) (Group 1), 13 had straight back (Group 2), and 33 had pectus excavatum (Group 3). Twenty five of the 80 patients (31 per cent) had evidence of MVP: 22 by echocardiographic criteria and three by phonocardiographic criteria. The incidence of MVP in this predominantly male population was substantially higher than that reported in the general adult population. Thoracic skeletal abnormality is an important nonauscultatory feature of mitral valve prolapse syndrome. The association between TSA and MVP may be a manifestation of a single connective tissue defect during embryonic development of the bony thoracic cage and the atrioventricular valves. All patients with TSA, even when asymptomatic

should be screened for MVP by noninvasive investigations. The recognition of MVP in patients with TSA may be of potential value in prevention of life-threatening endocarditis and cardiac arrhythmia.

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Cross-sectional echocardiographic spectrum of papillary muscle dysfunction

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Two major pathophysiologic mechanisms were first proposed by Burch and colleagues in 1963 to link the development of mitral regurgitation to dysfunction of the papillary muscles. First prolapse of the mitral valve leaflet could occur as synergistic contraction of the papillary muscles was lost as a consequence of ischemia or fibrosis. Second, incomplete valve leaflet coaptation could result from the loss of the normal spatial orientation of the papillary muscles as a consequence of ventricular dilatation or ventricular aneurysm formation.

Until now M mode echocardiography has not been able to distinguish these two distinct mechanisms of papillary muscle dysfunction. The ... introduction of a new cardiac imaging system has provided better anatomical definition of the mitral valve apparatus and permitted direct visualization of the papillary muscle–chordal structure It has been emphasized that this new technique is more sensitive than M mode echocardiography for the diagnosis of mitral valve prolapse, valvular vegetation and flail mitral leaflet. However thus far there have been no definitive cross-sectional echocardiographic criteria for the diagnosis of papillary muscle dysfunction.

The purpose of this communication is to present the echocardiographic findings in 14 patients in whom papillary muscle dysfunction was suspected to contribute to mitral regurgitation.

Methods and materials

Cross-sectional echocardiograms were recorded from 14 patients with mitral regurgitation due to papillary muscle dysfunction (Group A) and 40 patients without angiographic evidence of mitral regurgitation (Group B) None of the 54 patients had a clinical history or physical findings suggestive of rheumatic or congenital valvular disease, myxomatous valve degeneration, idiopathic hypertrophic subaortic stenosis, bacterial endocarditis, or chordal rupture. The patients ranged in age from 12 to 74 years. Forty three were male and 11 were female.

Pertinent clinical information from Group A patients is listed in Table I. All 14 patients had an apical holosystolic murmur (Grade 2 to 4/6). Eight of the 14 patients underwent cardiac catheterization in the course of routine clinical evaluation. Mitral regurgitation was evident on left ventricular cineangiography in all eight patients. All patients in Group A had conditions known to predispose to the development of papillary muscle dysfunction. Ten of the 14 patients had a clinical diagnosis of coronary artery disease. Of these patients, seven had electrocardiographic evidence of a prior myocardial infarction Four of the 14 patients had hypertensive cardiovascular disease. Ten of the 14 patients had evidence of left ventricular enlargement on M-mode echocardiography or left ventriculograms.

In all 14 patients, the diagnosis of papillary

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Table I Clinical and cardiac catheterization findings

Patient no. & initials	Age	Sex	Clinical diagnosis	ECG	Cardiac catheterization: LVG	Cardiac catheterization: Coronary artery lesions (more than 75% occlusion)
1 A. F	73	F	HBP	LVH		
2 L. M.	41	M	CAD	IMI	Akinesis of inferior wall 2+ MR	RCA
3 M. B.	56	F	HBP CAD	LVH	Diffuse hypokinesis 2+ MR	Normal coronary arteries
4 L. H.	54	M	CAD	LVH, IMI	Diffuse hypokinesis 2+ MR	RCA, LAD, CX
5 J N	4	M	CAD	LBBB	Diffuse hypokinesis 2+ MR	CX
6 W E.	54	M	CM	LVH	Diffuse hypokinesis with dilatation, 3+ MR	Normal coronary arteries
7 V G	62	F	metastatic cancer	low voltage nonspecific ST T changes		
8 R. N.	44	M	CM	1 AV block LVH		
9 A. M.	55	M	CAD HBP	AMI, IMI		
10 C. C.	56	M	CAD	IMI	Aneurysm of infero-posterior wall, 3+ MR	RCA, LAD, CX
11 J. M.	53	M	CAD	IMI	Aneurysm of infero-posterior wall, 1+ MR	RCA, LM, LAD, CX
12 J. S.	60	M	CAD	AMI	apical aneurysm, 2+ MR	LAD
13 C. M.	65	M	CAD	IMI		
14 E. W	65	M	CAD HBP	LVH		

Abbreviations: HBP = hypertension, ECG = electrocardiogram, IMI = inferior myocardial infarction, AMI = anterior myocardial infarction; LVG = left ventriculography; MR = mitral regurgitation, LAD = left anterior descending artery; LM = left main coronary artery; CAD = coronary artery disease; CM = cardiomyopathy; LVH = left ventricular hypertrophy; LBBB = left bundle branch block; RCA = right coronary artery; CX = circumflex coronary artery

muscle dysfunction was made on the basis of clinical evidence of mitral regurgitation known predisposition to papillary muscle dysfunction, and the absence of other conditions known to produce mitral regurgitation.

All 40 patients in Group B had undergone cardiac catheterization. None of these patients had evidence of mitral regurgitation on left ventriculography Ten of the 40 patients had normal coronary arteries and normal left ventricular function. Twenty-seven of the 40 patients had coronary artery disease, as identified by selective coronary cineangiography Eleven of these 27 patients had normal left ventricular function, eight had segmental wall abnormalities, and eight had a discrete ventricular aneurysm.

Echocardiographic techniques.

A. M mode echocardiography A Smith Kline Ultrasonoscope (Ekoline 20A) equipped with a 2.25 MHz focused transducer with a repetition rate of 1,000 impulses/second was used and permanent records were obtained on a multichannel oscilloscopic recorder (Honeywell 3820) at paper speeds of 25 and 50 mm./second. An M mode echocardiographic scan from the aorta to the left ventricular apex was routinely performed.

B. Cross-sectional echocardiography All cross-sectional echocardiograms were recorded using a commercially available 84 degree phased array imaging system (Varian V-3000 ultrasonograph). The transducer contained 32 precisely mounted piezoelectric crystals in a tight linear array operating at 2.25 MHz. The image was displayed in real-time at a rate of 30 scans/second. The images thus produced were recorded on a 1 inch video cassette which could be subsequently reviewed in real time, slow motion, or single frame presentation. A still frame of the video tape recording was photographed using Polaroid film.

The study was performed by the technique

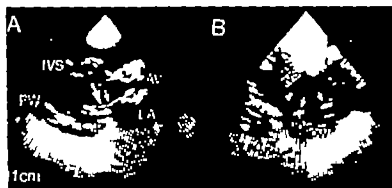


Fig. 1 Normal cross-sectional echocardiogram. Long axis (*A*) and short axis (*B*) views. Each frame was recorded in late systole. In *A* coaptation of the anterior and posterior mitral leaflets takes place at their free edges (*large arrow*) and slight arching toward each other is noted (*small arrow*). In *B* the papillary muscles are visualized in short axis (*two white arrows*). The posteromedial papillary muscle is located on the left and the anterolateral papillary muscle on the right. The echo density of the papillary muscles is similar to the adjacent myocardium. IVS = interventricular septum PW = posterior left ventricular wall; AV = aortic valve; LA = left atrium. The same abbreviations are used in Figs. 2 through 8.

described by Kisslo and associates. The transducer was initially placed in the third, fourth, or fifth intercostal space to the left of the sternum with a beam plane parallel to the long axis of the heart. On this view the heart was scanned from the aorta (*displayed on the right side of the image*) to the left ventricle (*on the left*) (Fig. 1A) The transducer was then rotated 90 degrees to a position perpendicular to a long axis to record a short axis of the left ventricle at the level of the papillary muscles (Fig. 1B)

In the normal heart (Fig. 1) coaptation of the anterior and posterior mitral leaflets occurs just below the mitral annulus (*large white arrow* in Fig. 1A) During systole, the leaflets arch slightly toward the left atrium but never move beyond the mitral annulus. Thus, the body of the anterior leaflet develops a slight convexity toward the left atrium (*small white arrow* in Fig 1A). By tilting the transducer slightly medially or laterally in the long axis view the papillary muscles (posteromedial or anterolateral) can be visualized together with the chordae tendineae and the mitral valve (see Figs. 2, 5, and 7)

In the short axis view frames of the left ventricle the papillary muscles are seen in cross-section as shown in Fig. 1B The posteromedial papillary muscle is seen on the left of the image and the anterolateral papillary muscle on the right (*white arrows* Fig. 1B) Normally these papillary muscles are of the same echo density as the adjacent left ventricular myocardium and ventricular septum.

Results

Group A.

1 Papillary muscle dysfunction secondary to papillary muscle fibrosis with mitral valve prolapse (Type 1). In three patients (cases 1 2, and 3) mitral valve prolapse was suggested on cross-sectional echocardiograms. Late systolic buckling of the anterior mitral leaflet toward the left atrium was seen at end-systole in Case 1 (*horizontal arrow* in Fig. 2B) while in Cases 2 and 3, both leaflets show a late systolic superior motion above the mitral ring (*indicated by black line* in a diagram of Fig. 3B) into the left atrium.

In all three patients, fibrosis or calcification of the papillary muscles was suggested by the abnormal echo density as compared to the adjacent myocardium (Figs. 2 and 3) The abnormal papillary muscles do not appear to shorten or contract throughout systole in the long axis view frames (in Fig. 2) Furthermore, an abnormally dense papillary muscle could be identified in the short axis view: In Case 1 the anterolateral papillary muscle (Fig. 2C), and in Case 2, the posteromedial papillary muscle (Fig. 3C).

The pattern of mitral valve prolapse could not be demonstrated on M mode echocardiography in these three cases. Reduced motion of the infero-posterior wall was obvious by echocardiography and by left ventriculography

2. Papillary muscle dysfunction associated with abnormal mitral valve coaptation in ventricular aneurysm (Type 2) and dilatation

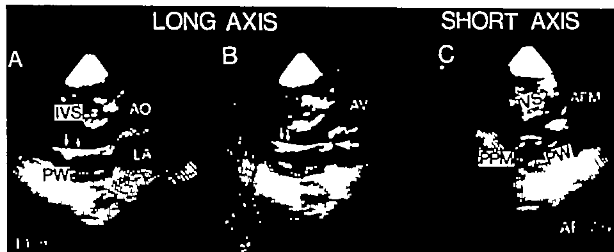


Fig. 2. Cross-sectional echocardiograms from Case 1. *Panels A* and *B* represent long axis view frames (*A*, midsystolic; *B*, late systole), and *panel C* short axis view frame at the level of the papillary muscles (late systole). Echoes from the papillary muscle (*vertical arrows*) on the long axis frames (*A* and *B*) appear abnormally dense, in relation to the interventricular septum and posterior wall, and do not shorten from panels *A* and *B*, suggesting papillary muscle fibrosis. The anterior mitral leaflet prolapses into the left atrium at late systole (*panel B, large arrow*). On the short axis view (*C*), this dense fibrotic papillary muscle is identified as anterolateral (*APM*). The posteromedial papillary muscle (*PPM*) exhibits less density than *APM*.

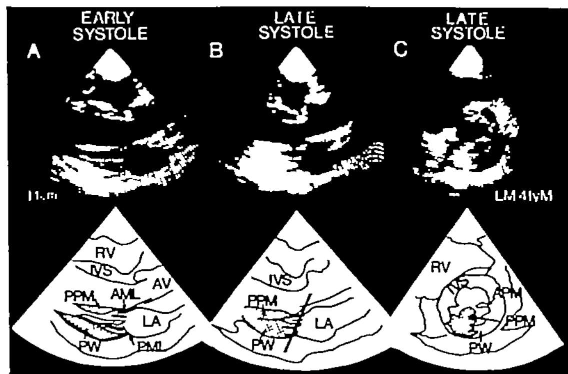


Fig. 3. Cross-sectional echocardiograms and schematic diagrams from Case 2. *Panels A* and *B* represent long axis frames (*A*, early systole; *B*, late systole), and *panel C* short axis frame (late systole). Both anterior (*AML*) and posterior (*PML*) mitral leaflets move superiorly towards the left atrium during systole (*from panel A to B*). In late systole (*panel B*) the entire mitral valve is seen slightly above the mitral annulus (*solid black line*). The posteromedial papillary muscle and the adjacent posterior wall exhibit abnormally dense echo reflections (*indicated by hatched areas* in diagrams of panels A, B and C). *Dotted lines* in panels A and B demarcate the pericardium.

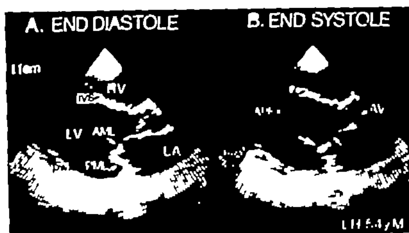


Fig 4. Cross-sectional echocardiograms from Case 4. Note a markedly dilated left ventricular cavity (LV) with diminished contractility. There is no appreciable change in ventricular configuration from end-diastole to end-systole. At end-diastole (left), the point of mitral valve coaptation is dislocated inferiorly toward the ventricular apex. During systole, the normal motion of the mitral valve toward the left atrium is not observed, and the point of coaptation remains inferior and displaced towards the apex of the ventricle at end-systole (large arrow in the right panel). In addition, basal part of the anterior mitral leaflet (AML) appears as convex curve towards the LV cavity (small arrow in the right panel).

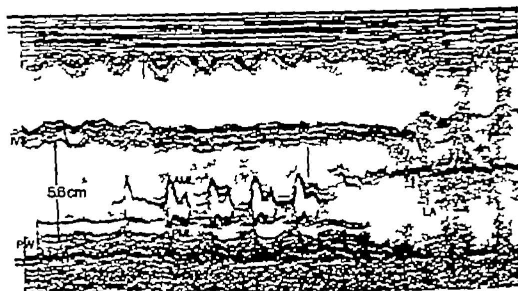


Fig 5. M-mode echocardiographic scan from the left ventricle to the aorta and the left atrium in Case 7. Motion of the interventricular septum and the posterior wall is diminished, but the left ventricular cavity is only slightly dilated (5.6 cm).

(Type 3) In nine patients, the entire mitral valve structure appeared to be abnormally tethered toward the apex of the left ventricle (Figs. 4 to 6). During systole the mitral valve did not move toward the mitral annulus. At end-systole the coaptation of the mitral valve was still displaced toward the left ventricular apex (large white arrow in Fig. 4B). In addition, the basal portion of the anterior mitral leaflet presented a convex curve toward the left ventricular cavity throughout systole (small arrow in Fig. 4B); this appearance of the mitral valve clearly contrasted with the normal curve of the anterior mitral valve leaflet during systole which was convex towards the left atrium[14] (see Fig. 1A).

Among these nine patients, six patients demonstrated generalized hypokinesis of the left ventricle with dilatation on M mode echocardiograms and/or ventriculograms (Cases 4 through 9), and three patients demonstrated discrete ventricular

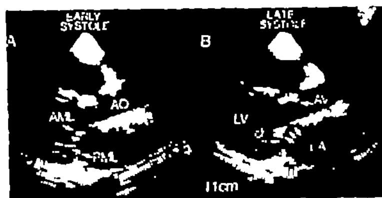


Fig. 6 Cross-sectional echocardiograms (long axis frames) from Case 7 *Panel A* represents an early systolic frame and *panel B* represents late systolic frame Note the convex curve of the anterior mitral leaflet towards the ventricle at late systole (*small arrow* in panel B).

aneurysms (Cases 10 through 12) In both patients with a large inferoposterior wall aneurysm (Cases 10 and 11) the point of mitral valve coaptation was displaced not only inferiorly toward the apex of the heart, but also posteriorly toward the aneurysm (not shown) The dislocated papillary muscles in these cases appeared to move with the aneurysm producing inferoposterior traction on the mitral valve. An abnormal inferior coaptation similar to that seen in the patients with a diffusely dilated left ventricle was observed in a patient with a large apical aneurysm (Case 12).

Inferiorly displaced leaflet coaptation could be seen also in the absence of marked ventricular dilatation. Figs. 5 and 6 were recorded from a patient who developed acute congestive heart failure following Adriamycin therapy for metastatic cancer (Case 7). Despite the absence of left ventricular enlargement in the M mode echocardiograms (Fig. 5), the long axis view of the cross-sectional echocardiograms (Fig. 6) clearly showed a pattern of abnormal inferior mitral valve coaptation. Also note the convex appearance of the anterior mitral leaflet toward the left ventricle (*three white arrows* in Fig. 6B). Therefore, marked ventricular dilatation per se did not appear to account for the abnormal mitral coaptation. Left ventricular wall motion was generally diminished both on M mode and on cross-sectional echocardiography (Figs. 5 and 6)

3. Papillary muscle dysfunction seconday to combined mitral valve prolapse and abnormal coaptation (Type 4). In two patients, abnormal mitral valve coaptation was seen, together with papillary muscle fibrosis and mitral valve prolapse. In one instance (Fig. 7) it was possible to visualize the long axis of the posteromedial papillary muscle from its base to its apex. In Figure 7*A*, two separate heads of the posteromedial papillary muscle receive the chordae tendineae from both the anterior and posterior mitral leaflets (*Nos. 1* and *2* in Fig. 7*A*). At the onset of systole the point of mitral valve coaptation was abnormally inferior and remained in this position throughout systole (Fig. 7*B* and *C* *white arrows*) while the body of the posterior mitral leaflet prolapsed into the left atrium beyond the mitral annulus (*dotted lines*) at end-systole (*small black arrow* in Fig. 7C diagram). Note that the papillary muscle and inferoposterior wall does not contract during systole.

Table II

	Normal MV no PM fibrosis	*PM fibrosis*	*Excessive superior systolic motion of MV*	*Abnormal MV coaptation*
Normal (10 pts)	10/10	0/10	0/10	0/10
CAD with normal LV (11 pts)	9/11	2/11	2/11	0/11
CAD with segmental wall abnormality (8 pts)	7/8	1/8	0/8	0/8
Dilated LV aneurysms (8) cardiomyopathy (3) (11 pts)	10/11	0/11	0/11	1/11
	36/40	3/40	2/40	1/40

Abbreviations CAD = coronary artery disease; LV = left ventricle MV = mitral valve; PM = papillary muscle. pts = patients.

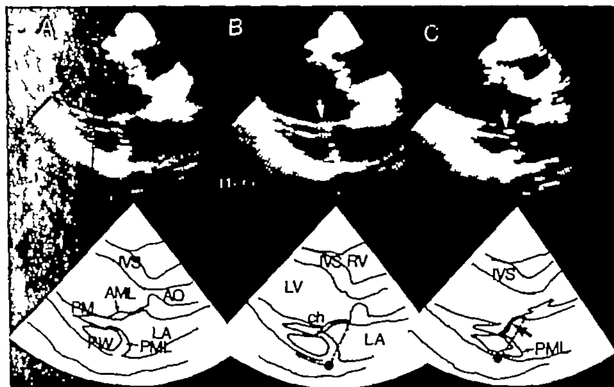


Fig. 7. Cross-sectional echocardiograms (long axis view) and schematic diagrams from Case 11. *Panel A* is taken in late diastole, and *panels B* and *C* are recorded during early and late systole, respectively. The posteromedial papillary muscle *(PM)* and the inferoposterior left ventricular wall are akinetic. The point of mitral valve coaptation is abnormally displaced toward the left ventricular apex (*white arrows* in *B* and *C*), and the anterior mitral leaflet *(AML)* exhibits convex appearance toward the ventricle throughout systole (*large black arrow* in the diagram of panel C). In contrast, the posterior mitral leaflet prolapses into the left atrium (indicated by small *black arrow (PML)* in the diagram of panel C).

On the short axis view the posteromedial papillary muscle echo appeared abnormally dense in relation to the anterolateral papillary muscle and the adjacent myocardium (not shown).

Group B

The angiographic and cross-sectional echocardiographic findings from 40 patients who did not have mitral regurgitation on catheterization are listed in Table II. None of the ten patients with normal left ventricles demonstrated either mitral valve prolapse or abnormal mitral coaptation. Of the 11 patients with coronary artery disease and normal left ventricular contractility two patients revealed papillary muscle fibrosis with mitral valve prolapse on cross-sectional echocardiograms. One of these patients showed diffuse right coronary artery narrowing, and M mode echocardiographic and angiographic evidence of prolapse of the posterior mitral leaflet. Among eight patients with coronary artery disease and segmental wall asynergy one patient with inferoposterior hypokinesis had papillary muscle fibrosis, but showed no evidence of mitral valve prolapse. In this patient, the systolic motion of the mitral annulus towards the apex appeared to be decreased. In only one of the 11 patients exhibiting a discrete ventricular aneurysm or ventricular dilatation was abnormal mitral valve coaptation observed without evidence of mitral regurgitation.

In all, only four of the 40 patients demonstrated abnormal mitral valve patterns without mitral regurgitation.

Discussion

Burch and colleagues first introduced the concept that dysfunction of the papillary muscles due to asynergistic contraction or malalignment could result in mitral regurgitation. A lack of synergistic contraction associated with inadequate restraint on the mitral leaflets allows the leaflets to evert into the left atrium as the distance between the ventricular apex and the mitral annulus decreases during systole. Papillary

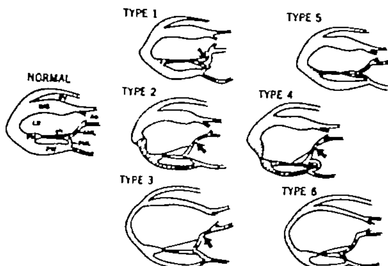


Fig. 8. Diagrammatic illustrations of various patterns of mitral valve abnormality associated with papillary muscle dysfunction (Types 1 through 4). *Type 1*, Noncontractile papillary muscles in the ventricle with normal long axis shortening during systole leading to mitral valve prolapse. *Type 2* (LV aneurysm) and *Type 3* (generalized left ventricle dilatation), Normal contraction of the papillary muscles in the ventricle with limited long axis shortening producing displacement of the point of mitral leaflet coaptation towards the apex of the left ventricle. *Type 4*, Mitral valve prolapse and inferior point of valve coaptation in case with inferior wall aneurysm and papillary muscle fibrosis. *Type 5*, Noncontractile papillary muscle and decreased long axis shortening of the ventricle with the absence of mitral valve prolapse. *Type 6*, Normal papillary muscle contraction and long axis shortening in dilated left ventricle with normal mitral leaflet coaptation.

muscle necrosis or fibrosis secondary to ischemia is the most frequent cause of this type of abnormality.

On the other hand, too much restraint on the mitral leaflets may pull the leaflets away from the mitral annulus into the left ventricle resulting in an improper valve coaptation and thus, mitral regurgitation. This situation may occur with diffuse ventricular dilatation, or with an aneurysm of the ventricular wall adjacent to the papillary muscles. Under these circumstances, the length of the papillary muscle–chordae apparatus becomes too short in relation to the long axis of the ventricular cavity and abnormal coaptation of the mitral valve cusps takes place in the body of the ventricle. In addition, lateral displacement of the papillary muscles diminishes the force producing cusp approximation during contraction, favoring the development of mitral regurgitation.

Observations in the present study provided strong supportive evidence for the occurrence of these two mechanisms in patients with mitral regurgitation due to papillary muscle dysfunction.

Fig. 8 summarizes the cross-sectional echocardiographic patterns associated with mitral regurgitation in the present study. Papillary muscle fibrosis with inadequate shortening may permit excessive systolic superior motion or prolapse of the mitral leaflets (Type 1, Figs. 2 and 3). Incomplete coaptation of the mitral valve due to displacement of the point of coaptation towards the apex of the ventricle may be seen in the presence of a discrete left ventricular aneurysm (Type 2) or left ventricular dilatation (Type 3, Fig. 4). The anterior leaflet of the mitral valve in these cases presents a convex curve towards the left ventricular cavity (*small white arrow* in Fig. 4B). Abnormal leaflet coaptation may also occur in the presence of leaflet prolapse (Type 4, Fig. 7).

These findings could be considered specific for papillary muscle dysfunction, as only four of the 40 patients without mitral regurgitation (Group B) demonstrated one of these patterns. There were no false-positive diagnoses in the ten normal patients in Group B. Two patients with severe coronary disease had papillary muscle fibrosis and excessive superior motion of the mitral valve leaflets without angiographic evidence of mitral regurgitation, and most likely represent papillary muscle dysfunction that is not clinically manifest as the degree of prolapse is not sufficient to produce mitral regurgitation.

Abnormal inferior coaptation was observed in only one patient in Group B which included ten patients with marked ventricular dilatation and/or ventricular aneurysm. It would therefore appear unlikely that dilatation per se produces abnormal mitral valve coaptation. This conclusion is reinforced by the findings shown in Fig. 6 where a Type 3 papillary muscle dysfunction pattern and mitral regurgitation were observed in a patient with a relatively small left ventricular cavity. It is suggested that the degree of long axis shortening of the ventricle could considerably modify the effects of LV dilatation in papillary muscle dysfunction. Normal long axis shortening could permit normal cusp closure despite an increase in left ventricular cavity size (Type 6) as seen in ten of the 11 patients with ventricular aneurysm or dilatation in Group B. Conceivably a marked decrease in long axis shortening due to left ventricular dysfunction could account for a disproportionately short papillary muscle–chordal structure to maintain normal valve coaptation even in the absence of striking ventricular dilatation (as in Case 7).

In a similar fashion, normal valve coaptation may be maintained in the presence of fibrosis of a papillary muscle if long axis shortening of the ventricle is diminished. In this situation, the appropriate papillary muscle–mitral valve distance would be maintained and prolapse of the mitral leaflets prevented (Type 5). This pattern was observed in one patient with coronary artery disease and inferoposterior wall hypokinesis in Group B (see Table II).

Although the exact incidence of mitral valve prolapse associated with coronary artery disease remains uncertain, Devereau and associates[22] found only 12 patients (6 per cent) with significant obstructive coronary artery disease among 218 patients reported in the literature with this combination. This incidence, however, could reflect the chance association of two common diseases.[22] Nevertheless, there has been recent evidence suggesting that mitral valve prolapse could result from papillary muscle dysfunction. In a recent angiographic study of 95 patients with coronary artery disease prolapse of *the posterior mitral leaflet was attributed to* papillary muscle dysfunction in 30 patients. In two of these patients who underwent aortocoronary bypass surgery, left ventricular contractility improved and the preoperatively identified mitral valve prolapse disappeared. Roberts and Cohen described a case of myocardial infarction in whom the anterior mitral leaflet was found to herniate into the left atrium but the leaflets and chordae tendineae appeared normal. Forrester and co-workers[24] reported cases with mitral regurgitation in acute myocardial infarction in whom mitral valve prolapse was shown by left ventriculography. Postmortem examination in those patients revealed extensive necrosis of the papillary muscles, without alteration of the mitral valve and chordae tendineae.[25] In the patients with late systolic murmurs described by Cheng, severe occlusive coronary artery disease and ischemic and fibrotic changes in one or both papillary muscles were demonstrated. Thus it seems reasonable to state that mitral valve prolapse related to papillary muscle dysfunction does exist and represents a heterogeneous spectrum of the mitral valve prolapse syndrome in which different pathophysiologic mechanisms account for this abnormality.

Auscultatory findings may give some insight into the etiologic factors of mitral valve prolapse. In the series reported by Scampardonis and colleagues[26] and by Gulotta and associates,[27] most of the patients with characteristic midsystolic clicks and late systolic murmurs *had normal* coronary arteries. In contrast, none of the 30 patients reported by Aranda and co-workers[23] in whom papillary muscle dysfunction was attributed to mitral valve prolapse, had systolic clicks, and only five had early or midsystolic apical murmurs. However midsystolic clicks may occur in mitral regurgitation associated with coronary artery disease.[28]

The presence of fibrosis of the papillary muscles on cross-sectional echocardiography could suggest the etiologic diagnosis of papillary muscle dysfunction patients with mitral valve prolapse. Although sensitivity or reliability of the cross-sectional echocardiographic technique to detect fibrosis or calcification remains to be determined, we feel that an unusually bright and dense appearance of the papillary muscle with reference to the adjacent myocardium associated with *absent systolic shortening can indicate* pathological abnormality of the papillary muscles (Figs. 2 and 3).

The incidence of papillary muscle fibrosis in a

group of patients with mitral valve prolapse syndrome has yet to be determined and is now under investigation.

Summary

Cross-sectional echocardiography identified two abnormal patterns of mitral valve closure in 14 *patients with mitral regurgitation due to papillary muscle dysfunction* (1) in three patients with an akinetic inferior-posterior wall but normal cavity size papillary muscle fibrosis was associated with late systolic mitral valve prolapse and (2) in nine patients with ventricular dilatation or ventricular aneurysm, the point of *mitral valve coaptation was displaced towards* the apex of the left ventricle. In two of these patients both abnormalities were observed.

In contrast, abnormal patterns were identified in only four of a group of 40 patients without angiographic evidence of mitral regurgitation (10 normal 27 coronary artery disease three, congestive cardiomyopathy). Thus, *cross-sectional echocardiography* can be useful to identify *mitral* regurgitation secondary to papillary muscle dysfunction.

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Table II Aprindine therapy

Patient	Most recent 24 hour recording		Oral aprindine dose	Aprindine serum concentration (mg./dl)	VT on treadmill exercise test
	VT	PVC's/24 hrs.			
1.	None	560	40 mg. Q 12 hr	1.34	None
2.	None	786	50 mg. Q 12 hr	0.55	None
3.	None	0	50 mg. Q 12 hr.	0.94	None
4.	None	1,017	50 mg. Q 8 hr	1.21	None
5.	None	809	40 mg. Q 8 hr	0.38	None
6.	None	3,228	50 mg. Q 8 hr	1.30	None
7	None	4,518	50 mg. Q 8 hr.	0.95	None

patients. While receiving aprindine therapy daily samples for serum drug concentrations[21] were obtained for one week, twice weekly until discharge, then weekly for one month and monthly thereafter

Hemoglobin, hematocrit, white blood cell count, and platelet counts were performed during the control period, weekly for 16 weeks and then monthly Serum concentrations of sodium potassium chloride, carbon dioxide content blood urea nitrogen, glucose, total protein, albumin, calcium, phosphorus, total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase lactic dehydrogenase, creatinine, creatine phosphokinase, and cholesterol were obtained during the control period and monthly thereafter

Twenty four hour Holter recordings were obtained continuously (Avionics model 445, 2-channel recorder) during the patient's entire hospitalization, once a week for one month, and then monthly Tapes were analyzed for the number of premature ventricular extrasystoles and episodes of ventricular tachycardia or ventricular fibrillation per 24 hours (Avionics model 660A scanner) by an independent agency that had no knowledge of the patient's history

Treadmill exercise testing was performed in each patient after stabilization on a dose of aprindine that produced the greatest antiarrhythmic effect as judged by a 12 lead ECG and CCU monitoring, and the least number of side effects.

Measurements The duration of the PR interval, QRS complex and QT $\frac{(QT)}{(RR)}$ interval were measured directly from the 1 lead ECG at 25 mm. paper speed Measurements were taken from the lead exhibiting the longest duration for each parameter and the control tracing was then compared with the same lead in the ECG recorded while the patient received aprindine.

Criteria for response The response of each patient to aprindine therapy was divided into the following categories based on data obtained from the 12 lead ECG 24-hour monitor recordings in the CCU Holter recordings, and the treadmill exercise test. (1) No episodes of ventricular fibrillation, (2) No episodes of ventricular tachycardia, (3) Ventricular tachycardia of no more than three or four complexes in duration, and associated with no symptoms. In addition, the frequency of premature ventricular extrasystoles per 24 hours was tabulated. Ventricular complexes present during ventricular tachycardia were included in the total premature ventricular extrasystole count.

Anthropometrics, Haddonfield

Results

Six of the seven patients had physical findings compatible with mitral valve prolapse and these same six patients also had evidence of mitral valve prolapse on M mode scan as well as with a two-dimensional echocardiogram. Two of these patients also had angiographic evidence of mitral valve prolapse while one patient met angiographic criteria only

Aprindine resulted in a 91 per cent reduction of the total number of premature ventricular extrasystoles per 24 hours, from 13,178 ± 5,390 to 1,557 ± 626 (mean ± standard error) (p = .05) (Table II, Fig. 1) when the control 24-hour recording was compared with the 24-hour recording obtained at the time of the most recent follow up visit. All patients had two or more episodes of ventricular tachycardia on the control 24-hour ECG recording prior to aprindine therapy (Table I) No patient demonstrated ventricular tachycardia on the 24-hour ECG at the time of

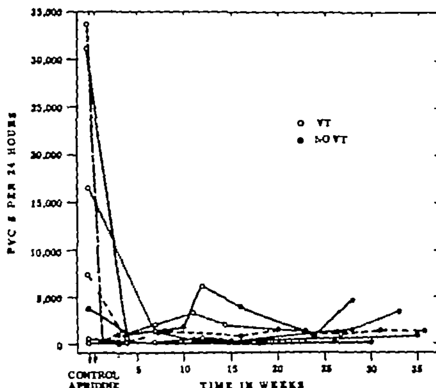


Fig. 1 Total PVC's per 24 hours versus time after aprindine therapy Open circles indicates that at least one episode of ventricular tachycardia occurred, but in no instance were more than three such episodes present during a 24-hour recording on aprindine. Closed circles indicate that no episodes of ventricular tachycardia occurred.

the most recent clinical evaluation (Table II). However as seen in Fig. 1 a number of patients experienced ventricular tachycardia earlier in their course of aprindine therapy In those patients, three or four consecutive premature ventricular extrasystoles at rates greater than 100 per minute comprised the ventricular tachycardia, and no patient had more than three such episodes in any 24 hour period. Patients who had the largest number of premature ventricular extrasystoles per 24 hours in the control recording exhibited the greatest reduction in subsequent PVC frequency on aprindine therapy All patients underwent submaximal treadmill exercise testing while receiving aprindine and no patient developed ventricular tachycardia during or following exercise.

Duration of follow-up ranged from three to 36 weeks (mean 27 weeks) Aprindine maintenance dosage ranged from 80 to 160 mg. per 24 hours (121 ± 11 mg., mean ± S E) Mean serum concentration of aprindine was 0.85 ± 0.14 mg. per cent, (mean ± S.E.) and ranged from 0.38 to 1.34 mg. per cent.

Side effects. Side affects, summarized in Table III, were arbitrarily divided into those which occurred early (less than 16 weeks of aprindine therapy) and those which occurred late (greater than 16 weeks of aprindine therapy). After less than 16 weeks of therapy five patients exhibited intention tremor three patients experienced vertigo, and one patient each experienced dry mouth and nausea. After 16 weeks of therapy tremor was present in only two patients, both of whom had experienced intention tremor early Depression developed in an additional patient, but whether it was related to aprindine is not known. Both tremor and vertigo appear to be dose-related and responded to reductions (often as little as 10 mg. per day) in dosage. The serum concentration of aprindine and the dose at which neurologic signs or symptoms occurred varied greatly from one patient to another Meclizine decreased the severity of vertigo or abolished it entirely but did not affect the intention tremor Dry mouth and nausea subsided spontaneously No significant change occurred in any of the blood chemistries measured. One patient (Patient No. 1) developed a white blood cell count as low as 3,200 (range 3,200 to 5,000 with normal differ

Table III Side effects

	< 16 weeks	> 16 weeks
Tremor	6/7	2/6
Vertigo	3/7	0/6
Dry mouth	1/7	0/6
Nausea	1/7	0/6
Depression	0/7	1/6(?)

Table IV Electrocardiography

	PR interval		QRS duration		QT interval	
Patient	Control	Aprindine	Control	Aprindine	Control	Aprindine
1	.16	.17	.08	.09	43	44
2	.17	.17	.08	.08	42	43
3	.12	.16	.09	.10	40	40
4	.16	.20	.09	.11	45	43
5	.18	.20	.08	.08	42	43
6	.18	.21	.09	.12	46	46
7	.12	.16	.12	.11	44	42

WPW

ential) but has continued to receive aprindine. Her white blood cell count is still monitored weekly. Cholestatic hepatitis has been reported[33] to occur with aprindine, but in none of these seven patients did clinical or laboratory evidence of hepatotoxicity develop.

Electrocardiography. Results of electrocardiographic measurements are summarized in Table IV. Aprindine resulted in an increase in the PR interval and QRS duration, but no change in QT interval or heart rate. U waves were noted to be more prominent in patients receiving aprindine. The patient with Wolff-Parkinson-White syndrome (Patient No. 7) developed complete anterograde block in the accessory pathway on a repeat electrophysiologic study and supraventricular tachycardia could not be reinitiated. In this patient, the QRS complex narrowed during aprindine therapy due to anterograde block in the accessory pathway.

Discussion

The frequency of mitral valve prolapse in the asymptomatic general population is not settled. It has been reported to occur in [illegible] per cent of patients, depending on the criteria used to diagnose it, upon the sex and, possibly, upon the age of the population studied.[1] We chose multiple criteria to diagnose mitral valve prolapse in the present study and, in six of the seven patients, at least two of the three criteria chosen were fulfilled. Five of the seven patients had no other anatomic cardiovascular abnormality noted.

The frequency of life-threatening ventricular arrhythmias is difficult to assess in patients with mitral valve prolapse. When serious ventricular arrhythmias do result they often respond to therapy with propranolol.[2, 3, 8, 27-31]

Because all seven patients exhibited symptomatic, potentially life-threatening, ventricular arrhythmias, treatment was imperative. Conventional antiarrhythmic agents were tried and found to be unsuccessful either because the patient did not tolerate the drug(s), or because the arrhythmia was drug resistant. Unequivocal proof of drug resistance was difficult to achieve in this study since drugs were not given to the point of producing toxic side effects and blood concentrations were obtained in only a few patients prior to referral to our institution. At the very least, however, the present study indicates that the patients reported here did not respond to, or were intolerant of, conventional antiarrhythmic drugs in the doses listed (Table I) and were treated successfully with aprindine.

The electrophysiologic mechanisms responsible for ventricular arrhythmias in patients with mitral valve prolapse are unknown, but have been speculated to be related to repolarization (Q-T) abnormalities, physical factors associated with the prolapsing valve,[34, 35] and, possibly, to a segmental cardiomyopathy.[36-37] Why aprindine was so successful in this small series is unknown.

Three patients had prolonged QT intervals prior to drug therapy. Aprindine increased the QT interval in one patient, shortened it in another (by eliminating conduction over the accessory pathway in patient No. 7 with WPW syndrome), and resulted in no QT change in five patients. The fact that aprindine did not prolong the QT interval in this group may be of therapeutic importance.

Aprindine has been used to suppress both supraventricular and ventricular arrhythmias that did not respond to conventional drugs in patients with diverse types of cardiac problems.[38-44] Its electrophysiologic properties in humans as well as animals and isolated preparations have been thoroughly studied and reviewed recently. In one animal study aprindine

suppressed arrhythmias that conventional drugs failed to affect, thus suggesting a possible unique mechanism of action.[44]

In the current study though the patient population was small, aprindine therapy resulted in greater than 91 per cent reduction in the number (mean) of premature ventricular extrasystoles per 24 hours, marked reduction in the frequency and duration of ventricular tachycardia, prior to its total suppression and complete abolition of the symptoms associated with ventricular arrhythmias in all seven patients. It would therefore appear that therapy with oral aprindine provides a reasonable alternative to more invasive measures for suppressing drug resistant arrhythmias associated with mitral valve prolapse, such as overdrive pacing[8] and mitral valve replacement.

Unfortunately as with other drugs, aprindine exerts side effects which may limit its widespread use. However the neurologic problems are dose-related and, in most patients, a therapeutic dose can be usually achieved which produces minimal or no side effects. The development of agranulocytosis[45] is unpredictable and white blood cell counts must be obtained in all patients receiving aprindine and be followed closely

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Serotonin blockade during experimental coronary thrombosis

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In most cases of acute myocardial infarction, except in early sudden death, thrombosis of the coronary artery can be demonstrated at autopsy. This may be due to the high incidence of uncomplicated coronary atherosclerosis in the young adult and the finding that initiation of the thrombotic episode is almost exclusively the result of a rupture in the roof of an atheromatous plaque[1] in the endothelial lining. One of the substances released from platelets during thrombus formation is serotonin (5-hydroxytryptamine or 5-HT). Sullenberger and associates[2] demonstrated the release of this amine during in vivo venous thrombosis. Page and McCubbin showed that 5-HT has the ability to oppose neurogenic tone in the vascular smooth muscle. When neurogenic tone was normal or increased, 5-HT behaved as a vasodilator and when neurogenic tone was decreased it acted entirely as a powerful vasoconstrictor particularly on the venules. In addition to this amphibaric action on blood vessels, Fillion and colleagues suggested that the cardiac stimulatory effect of 5-HT is mediated by norepinephrine (NE), probably through a neural exchange of the two amines in the sympathetic nerve endings. Bulle[6] demonstrated an accumulation of serotonin in the myocardium of the isolated rabbit heart which peaked approximately three hours after experimentally induced thrombotic occlusion of the anterior descending coronary artery.

Platelet thrombi also are known to develop during the early stages of experimental coronary thrombosis within the ischemic microvasculature. Gladkova and Vasiliev[8] reported a rise of 5-HT concentration in coronary venous blood following coronary artery ligation in dogs. Dancoff and co-workers and Swedenborg[1] induced pulmonary vasoconstriction in dogs following experimental thrombosis, which they attributed to the effect of 5-HT. In both studies, the antiserotonin agent methysergide significantly blocked the vasoconstrictor effect and minimized associated hemodynamic responses. Methysergide acts peripherally and does not affect the central nervous system to any appreciable degree.[12] From the studies cited above, it would seem logical to infer then that retention of released platelet 5-HT in the myocardium at the time of thrombosis may have an effect on the microvasculature of the ischemic area. Since neurogenic tone is usually decreased in the ischemic myocardium, the increased concentration of 5-HT resulting from thrombotic occlusion may lead to localized vasoconstriction of the myocardial vessels in the affected area.

Following a short temporary occlusion of a major coronary artery small coronary vessels immediately dilate in an attempt to direct an increased compensatory blood flow to the affected myocardium. Their capacity however is usually insufficient to prevent infarction when blood flow is occluded for an extended period. Merrick and associates[13] demonstrated that retrograde flow and diastolic peripheral coronary pressure in an obstructed vessel are indirect measurements of the development of coronary collateral circulation. Bloor and White, in conscious dogs,

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showed that peripheral coronary pressure in the early stages after occlusion of either the circumflex or anterior descending branch of the main left coronary artery is not associated with increased retrograde flow. In other words, retrograde flow is a better index than pressure of the development of collateral vessels. Retrograde flow usually occurs approximately four days post-occlusion. The immediate availability and extent of collaterals at the time of occlusion could be an important determinant of infarct size. Higher flows in the border zones result in a larger area of survivable tissue. In the first hours following acute coronary occlusion, there is no clear-cut demarcation between normal myocardium of involved tissue and that irreversibly injured by ischemia.[14] The area of this initial ischemia is probably greater than the ultimate area of infarction.

The principal determinant of myocardial oxygen consumption is intraventricular pressure. Immediately after occlusion, contractile force decreases in the affected myocardium but gradually increases with time. Maroko and colleagues concluded from a study evaluating different factors influencing infarct size that interventions which enhance myocardial oxygen consumption increase the extent of ischemic injury and the quantity of necrotic tissue.

The infarction model which we selected for this study (see Methods section) was one in which a slowly occluding thrombus formed in the left anterior descending (LAD) branch of the main left coronary artery in the closed-chest dog. It was felt that this model would yield a greater concentration of 5-HT released from platelets involved in the thrombotic process than would be achieved by other methods.

The hypothesis of our study is that blockade of 5-HT released from both the primary (LAD) and distal secondary (microcirculation) thrombi may minimize the presumed vasoconstriction. This, then would reduce the ischemia in the affected myocardium and, hopefully would lead to a reduction in the final infarct size.

Methods

Preconditioned mature mongrel dogs ranging in weight from 20 to 25 kilograms were used in this study. The 18 dogs initially studied were divided equally into control and pretreated (methysergide) groups. In these earlier two groups cardiac output was determined by dye dilution technique. Central aortic pressure was recorded by catheter placed via the femoral artery into the aorta. Left ventricular dP/dt was recorded using an RC differentiating circuit coupled to a left ventricular catheter inserted through the femoral artery. Heart rate was calculated from the pressure tracing. Peripheral resistance and stroke volume were calculated from cardiac output and mean aortic pressure, and heart rate, respectively using standard formulae. Baseline, one, three, five hours, and 8 day recordings were obtained from each dog, following occlusion of the LAD. No blood samples for biochemical analysis were obtained from these 18 animals. Histological studies, however were performed on the hearts of those dogs which survived eight days.

Twelve additional dogs (six control and six pretreated) were studied subsequently. In these dogs, electromagnetic flow probes were used to measure cardiac output. A flow probe selected for chronic implantation was placed around the ascending aorta in each dog two weeks prior to the production of experimental thrombosis. In these 12 dogs, biochemical variables were followed. Blood samples were obtained from the great coronary vein to determine concentrations of sodium, potassium, calcium chloride, magnesium, lactate, pyruvate, creatine phosphokinase, lactic dehydrogenase, uric acid, 5-hydroxytryptamine, platelets, total lipids, and hematocrit. These samples were obtained from the great cardiac vein to avoid the dilution effect in peripheral venous blood samples. Hemodynamic variables measured were the same as in the first 18 dogs. However measurements were only made up to five hours following occlusion of the LAD.

The animals were sacrificed at the end of this time for gross and microscopic evaluation of each heart. The terms acute and chronic as used in this paper refer to those dogs followed up to five hours, and those followed for one and eight days, respectively.

The infarction model[15] used to produce the LAD thrombus was developed in our laboratory which consisted of selective placement of a (thrombogenic) helically-shaped copper wire into the LAD branch of the main left coronary artery via a double catheter system in the closed-chest dog. For this procedure the animals were anesthetized lightly with pentobarbital sodium (10 to 12 mg./Kg.). In this procedure, the top of the inner catheter holding the wire coil was inserted into

the left common carotid artery and passed retrograde to the ostium of the left coronary artery. Under fluoroscopic (image intensifier) control, it was directed into the LAD in the following manner. The outer catheter was held in a fixed position, and by pulling the inner catheter back, the tip of the outer catheter pushed against the wire, releasing it to float down the LAD. The wire had an over all diameter of approximately 1.5 to 2.0 mm. and length of 5 to 6 mm. Based on previous experience with dogs of the same size used in this study, this configuration consistently caused the wire to lodge in the mid LAD. The wire did not significantly alter or reduce blood flow initially. When the occluding thrombus began to form 15 to 20 minutes after release, coronary blood flow was first reduced and finally stopped. Occlusion was confirmed angiographically and by changes in the ECG (S-T segment) wave configuration. Using this model, it was possible to monitor the chain of events from initial ischemia to infarction. The resulting infarction was secondary to the slowly occluding intracoronary thrombus. Thus, the model closely resembled the process often seen in humans, except for the presence of an usually preexisting atherosclerosis in the latter.

The experimental design for all dogs of both the control and pretreated groups was the same, except that in the latter methysergide* (100 μg/Kg., B.W.) was dissolved in 10 c.c. of physiological saline and intravenously infused 30 minutes before recording all baseline variables. In each dog, respiration was unassisted through a secured intratracheal catheter. Blood gases and pH were measured in arterial and venous blood before and at 1, 3, and 5 hours after occlusion. Usually only pH adjustments (bicarbonate ion) were required in the early acute stage.

For placement of catheters, the ventral surfaces of the neck and femoral skin areas were surgically prepared. Polyethylene catheters (5 Fr) were percutaneously inserted via the right femoral artery and vein, securing the tips in the thoracic aorta and inferior vena cava. Then a segment of both the left jugular vein and common carotid artery was freed from surrounding tissues, through a skin incision overlying these vessels. A double catheter system, as described above, was

*The generous supply of this drug by Sandoz, Ltd., is gratefully appreciated.



Fig. 1. X-ray photograph showing anatomical relationship of precordial ECG electrodes with the heart.

inserted in the jugular vein and the tip was advanced to the right atrium, under image intensification. The catheter was directed into the ostium of the coronary sinus and the tip of the inner catheter was advanced six to eight cm. into the great cardiac vein. Its position was confirmed by injecting contrast medium (Renografin-60) into the coronary vein and by the pO_2 level in blood samples withdrawn from this site.

For ECG mapping, the chest and extremities were prepared for the placement of the multiple precordial and standard limb electrodes (Fig. 1). Seven equidistant precordial electrodes were positioned via an elastic rubber strap across the chest between the base and apex of the heart as delineated by its shadow on the fluoroscopic screen (level A). The electrode sites extended between the right and left mid-axillary lines. This level was the approximate site of the occlusion produced by the thrombogenic wire. Another similar lead system (level B) was positioned and secured midway between the previously placed line of electrodes and the apex of the heart. These, together with the six standard limb leads, formed a 20-lead electrode system connected by cable to a Sanborn 500 electrocardiograph. The technique was the same for every dog in each group.

After each apparatus was properly placed, the femoral artery catheter was connected to a Statham p23Db pressure transducer and the electromagnetic flow probe was connected to a Statham 2202 flowmeter. Output signals of these two were connected to an Astrodata Physiologi

Table I. ΣS-T segment and ΣQ wave mean amplitudes from the 14 PM electrode sites (P to P)

Variable	Group	Condition	Level A (P P)	Level B (P -P)	Levels A + B (P P)
ΣQ waves	Control	Baseline	−1.8	−1.6	−3.4
		+5 Hours	−15.6	−11.6	−27.2
		+1 Day	−49.0	−61.4	−100.4
		+8 Days	−59.1	−55.4	−114.5
	Methysergide	Baseline	0.0	0.0	0.0
		+5 Hours	−5.2	−2.4	−7.6
		+1 Day	−29.1	−45.3	−74.4
		+8 Days	−15.9	−31.3	−47.2
ΣS-T segments	Control	Baseline	1.0	0.6	1.6
		+5 Hours	18.4	17.8	36.2
		+1 Day	14.4	16.8	31.2
		+8 Days	16.2	16.7	32.9
	Methysergide	Baseline	0.0	0.0	0.0
		+5 Hours	19.3	14.7	34.0
		+1 Day	12.9	13.9	26.8
		+8 Days	10.2	9.9	20.1

cal Monitoring System, visually followed by a dual beam Tektronic monitoring scope, and recorded on a Honeywell 1801 Visicorder. In the 18 dogs where dye–dilution (cardiogreen) cardiac output was used, the output signal (dye curve) from a Gilford densitometer was also connected to the Astrodata and Honeywell recording system. In a group of dogs (not a part of this study) there was a close correlation and no significant differences between the dye dilution and electromagnetic flow probe methods of determining cardiac output, where simultaneous recordings were made.

First, all baseline hemodynamic and ECG recordings were made. Coronary venous blood specimens were collected only in the second two groups of 12 dogs. After these were obtained, the thrombogenic wire was placed in the LAD as described above. All recordings were repeated and blood samples were obtained at ne three and five hours after complete obstructi n of the LAD was confirmed by ECG changes and selective coronary arteriography. The animals in the acute experimental groups were then k lled by an over dose of pentobarbital. Four heart m each group were removed at autopsy and ubmitted for gross and microscopic evaluati n the chronic experimental g oups, the w re sutured and bandaged, the instrumen n was discon nected, and the nimals ed to their cages. Hemodynamic rec d re repeated

one and eight days after coronary artery occlusion. Nine hearts from each group were removed after the eighth day for histological examination as in the acute experimental groups.

Results

In each dog there was evidence of ischemia present in the electrocardiogram within 3 minutes of placing the wire in the left anterior descending coronary artery. Subsequently S-T elevation, indicating progressive injury, occurred in most precordial leads with variable amplitudes, depending on the location of the electrodes. There was, however, a very marked difference in the amplitude of the S-T segment elevation between the control group and the methysergide pretreated animals. Table I shows the amplitudes of S-T segment elevation in the first five hours. There was evidence of significantly more injury pattern in the control group when compared to the methysergide pretreated group. The ΣS-T (Levels A and B) elevations was greatest at the fifth hour of occlusion in the control group which was slightly greater than the ΣS-T elevation in the methysergide pretreated group for the same time. The ΣS-T elevation in the methysergide group was about half of the sum for the control group at the eighth day. The ΣQ wave mean amplitudes measured over all precordial leads increased progressively in the control group, reaching a peak at the eighth day. The ΣQ wave mean amplitudes reached a maximum value at the first day following occlusion in the methysergide group, and decreased to approximately one-third of the control group value at the eighth day.

The corresponding biochemical changes are indicated in Tables II and III. The mean baseline coronary venous CPK and LDH enzyme concentrations are not significantly different between the control and methysergide pretreated groups (Table II). At the end of the five hours, the mean coronary venous CPK concentration increased threefold in the control group and only twofold in the methysergide pretreated group. The mean coronary venous LDH level increased in the control group but did not change in the methysergide pretreated group. These findings suggest significantly less myocardial injury and enzyme release in the methysergide pretreated animals in the early stages of LAD obstruction (up to five hours).

Serum lactate levels were different between the

Table II Mean concentrations of different biochemical variables measured in the coronary venous blood for both groups

Variables	Groups	Baseline (n = 6)	Time after occlusion: 1 hour (n = 6)	3 hours (n = 6)	5 hours (n = 6)
Lactate (mg/dL)	Control	12.9 ± 14.4	29.0 ± 13.2	13.6 ± 16.0	40.0 ± 27.2
	Methysergide	3.6 ± 3.8	5.0 ± 4.2	6.0 ± 4.8	10.0 ± 11.5
Pyruvate (mg./dL)	Control	0.4 ± 0.4	1.2 ± 0.9	1.8 ± 1.7	1.7 ± 1.5
	Methysergide	0.7 ± 0.2	0.8 ± 0.1	1.0 ± 0.2	1.5 ± 1.2
CPK (units/ml.)	Control	30 ± 9	na	na	90 ± 17
	Methysergide	36 ± 17	na	na	77 ± 34
LDH (units/ml.)	Control	161 ± 77	na	na	1056 ± 526
	Methysergide	258 ± 144	na	na	236 ± 132
Uric acid (mg./dL)	Control	0.4 ± 0.1	1.0 ± 0.7	1.5 ± 1.0	1.9 ± 1.1
	Methysergide	0.3 ± 0.1	0.4 ± 0.2	0.6 ± 0.4	1.4 ± 1.5
5-HT (µg/ml.)	Control	1.0 ± 0.7	1.3 ± 0.8	1.5 ± 0.7	1.9 ± 1.6
	Methysergide	1.3 ± 0.6	1.4 ± 0.6	1.5 ± 0.6	1.6 ± 0.7

Table III Mean concentrations of various biochemical elements measured in the coronary venous blood for both groups

Variables	Groups	Baseline (n = 6)	Time after occlusion: 1 hour (n = 6)	3 hours (n = 6)	5 hours (n = 6)
Sodium (meq./L.)	Control	154 ± 3.1	154 ± 4.8	156 ± 7.6	156 ± 9.2
	Methysergide	151 ± 2.8	156 ± 3.2	156 ± 3.3	156 ± 2.1
Potassium (meq./L.)	Control	3.6 ± 0.3	2.9 ± 0.7	3.3 ± 0.9	3.9 ± 1.0
	Methysergide	3.7 ± 0.5	3.6 ± 0.3	3.7 ± 0.6	3.5 ± 1.1
Calcium (meq /L.)	Control	10.1 ± 1.7	12.3 ± 2.7	10.8 ± 3.4	9.6 ± 2.1
	Methysergide	12.3 ± 2.1	11.9 ± 2.4	13.5 ± 4.2	11.3 ± 0.3
Chloride (meq /L.)	Control	96.7 ± 2.8	106.4 ± 8.6	107.2 ± 7.5	109.8 ± 1.2
	Methysergide	105.1 ± 4.2	103.0 ± 3.6	103.6 ± 2.5	104.0 ± 2.6
Magnesium (meq./L.)	Control	2.3 ± 1.0	2.5 ± 1.3	2.2 ± 1.2	2.0 ± 0.7
	Methysergide	1.3 ± 0.2	1.1 ± 0.2	1.2 ± 0.1	1.3 ± 0.2
Hematocrit (vol. %)	Control	43 ± 1.8	46 ± 3.4	46 ± 3.7	46 ± 3.8
	Methysergide	42 ± 4.7	43 ± 6.3	42 ± 6.2	39 ± 3.8
Platelets (10³/mm.)	Control	157 ± 21	125 ± 73	122 ± 65	136 ± 72
	Methysergide	209 ± 57	171 ± 70	162 ± 78	161 ± 85
Total lipids (mg./dl.)	Control	273 ± 63	256 ± 35	269 ± 23	360 ± 218
	Methysergide	280 ± 47	275 ± 52	282 ± 80	289 ± 63

control group and the methysergide treated group before coronary thrombosis was produced (baseline). Following coronary thrombosis, the mean lactate level increased significantly in the control group at the first ($p < 0.05$) third ($p < 0.01$) and fifth hour ($p < 0.01$) after coronary artery occlusion. In the methysergide pretreated group, there was a small but not significant increase of the lactate levels over the five hours of observation. Pyruvate levels were similar in the control and methysergide pretreated groups before coronary artery occlusion. Small increases were present in both groups following coronary artery occlusion, but the slight increase was significant ($p < 0.05$) only in the methysergide pretreated group at the third hour post-coronary arterial occlusion, probably due to the small standard deviations.

Uric acid levels were similar in the two groups at baseline, but in the control group the fourfold increase was significant ($p < 0.05$) at the third

Table IV Mean values for the hemodynamic variables followed in both groups

Variables	Groups	Baseline (n = 15)	Time after occlusion: 1 hour (n = 15)	3 hours (n = 15)	5 hours (n = 15)	1 day (n = 9)	8 days (n = 9)
Heart rate (beats/min.)	Control	177 ± 31	153 ± 27	150 ± 30	164 ± 34	167 ± 22	116 ± 40
	Methysergide	179 ± 28	156 ± 27	164 ± 22	178 ± 37	194 ± 20	143 ± 23
Cardiac output (L./min.)	Control	2.74 ± 0.9	1.70 ± 0.7	1.40 ± 0.5	1.33 ± 0.6	1.53 ± 0.3	2.7 ± 1.2
	Methysergide	3.86 ± 0.9	2.54 ± 0.7	2.30 ± 0.8	2.37 ± 0.8	2.43 ± 0.7	4.2 ± 1.1
Central aortic pressure (mm. Hg)	Control	125 ± 33	106 ± 42	111 ± 29	106 ± 37	95 ± 19	101 ± 18
	Methysergide	133 ± 38	115 ± 25	117 ± 27	168 ± 180	93 ± 25	111 ± 39
Total peripheral resistance (dynes-sec./cm.)	Control	4231 ± 1540	5578 ± 3015	6767 ± 2225	6740 ± 2400	5509 ± 1864	3499 ± 1213
	Methysergide	2967 ± 974	3895 ± 1364	4976 ± 3115	4202 ± 1979	2290 ± 996	2382 ± 712
dP/dt (mm. Hg/sec.)	Control	1200 ± 467	883 ± 472	948 ± 700	706 ± 342	737 ± 251	968 ± 309
	Methysergide	804 ± 346	575 ± 269	433 ± 86	836 ± 280	916 ± 284	1700 ± 358
Stroke volume (c.c./beat)	Control	15.7 ± 3	11.8 ± 4.6	9.3 ± 3.0	8.1 ± 2.7	9.3 ± 1.8	24.0 ± 6.2
	Methysergide	23.0 ± 6.2	17.2 ± 6.2	14.2 ± 5.3	14.2 ± 6.5	12.7 ± 3.5	21.2 ± 4.6

and the fifth hour post-occlusion. No significant changes in the uric acid level was demonstrated in the methysergide pretreated groups. 5-HT levels were not different in the two groups at baseline, but there was a greater increase in the control than in the methysergide pretreated group at the fifth hour post-occlusion.

The sodium, potassium, calcium, chloride, magnesium electrolytes (Table III) showed some variation in both groups but no significance between group differences was found in any of the groups during the pre- or post-occlusion periods.

The hematocrit showed a significant increase following coronary artery occlusion in the control animals but no significant change was present in the methysergide pretreated animals. The baseline hematocrit in the control group increased significantly ($p < 0.05$) the fifth hour. Peripheral blood hematocrit was obtained at baseline and at the fifth hour and was also significantly higher ($p < 0.01$) at the fifth hour in the control group as compared to the methysergide pretreated group.

Platelet concentrations and total lipids were also obtained in the coronary venous blood but no significant changes were found between the groups at baseline or up to five hours following coronary artery obstruction.

The hemodynamic changes are shown in Table IV. Six of the 15 animals studied in each group were followed for only five hours following coronary artery obstruction (acute group). They were then killed for histological examination of the heart. In the remaining nine dogs, hemodynamic measurements are available in eight control and eight methysergide pretreated animals one day after LAD occlusion and in six from each group eight days following occlusion. After the eighth day all nine dogs in each group were killed for histological examination. In the control group there was a significant decrease ($p < 0.05$) of the cardiac output from baseline after the first, third, and fifth hour following coronary artery occlusion. The cardiac output was depressed in the surviving eight dogs one day after coronary artery occlusion but increased to baseline levels by the eighth day following occlusion. In the methysergide pretreated group, there was a moderate decrease of the cardiac output at the third hour post-occlusion ($p < 0.05$). After this, the output increased and was not significantly different from baseline at one and eight days post-occlusion. Central aortic pressure and heart rate decreased in both groups following occlusion of the coronary arteries, but more significantly in the control group. Stroke volume and total peripheral resistance reflected these changes in that stroke volume decreased more in the control group than in the methysergide pretreated group while peripheral resistance increased more in the control group as compared to the methysergide pretreated group. Left ventricle dP/dt decreased in both control and methysergide pretreated groups from baseline during the first five hours of coronary arterial occlusion, but the decrease was

significant ($p < 0.02$) only in the control group.

The gross anatomical and histological examinations were performed using a single-blind procedure in a single-blind fashion and the hearts were only identified to the pathologist by code number In all of these hearts, there was an obstructive thrombus adherent to the wire lodged in the anterior descending coronary artery

Four control and four methysergide pretreated dogs were killed five hours after coronary arterial occlusion and the hearts were microscopically examined. The hearts were stained by hematoxylin-eosin technique. Early infarction was present with evidence of microscopic necrotic foci in two of the control hearts. One showed a well delineated acute myocardial infarction and one showed no microscopically identifiable lesion. In the four methysergide pretreated hearts, two showed small multiple microscopic foci consistent with early myocardial infarction and two had no significant lesions. The over-all impression of early myocardial infarction, when present, was less evident in the methysergide pretreated group than in the control group. Since five hours after coronary artery occlusion is too early for definite demarcation and necrosis because of the poorly defined lesions, it is not possible to evaluate any microscopic evidence of protection by methysergide at this early stage.

In the 18 hearts which were examined eight days following the coronary artery occlusion, all nine in the control group showed classical evidence of myocardial infarction with 90 to 100 per cent anucleated fibers in the affected myocardium. The nine hearts of the methysergide pretreated group showed a similar gross involvement, however there was only an average of 10 per cent anucleation of the myocardial fibers in the affected areas of each heart. There was a red discoloration in these fibers but the nuclei were present and cross striations were evident. In summary there was a distinct qualitative difference in the gross and microscopic myocardial tissue in six of the nine methysergide pretreated hearts at the end of the eighth day when compared to the control group

Discussion

The experiments described indicate that dogs pretreated with methysergide showed less myocardial injury in a closed-chest animal model of myocardial infarction produced by thrombotic occlusion of the left anterior descending coronary artery The ΣS-T segment elevations, conventionally taken as the index of ischemic injury during the acute phase (up to five hours post-coronary artery occlusion) was less in the methysergide pretreated animals than in the control group. In addition, there was significantly less increase of CPK and LDH in the coronary sinus blood of these dogs. The hemodynamic measurements during the first five hours reflected the protection of the ischemic myocardium to a lesser degree than would be expected from the ECG and enzyme changes. Cardiac output and stroke volume decreased in both groups, although to a lesser degree in the methysergide pretreated group. This decrease in the hemodynamic parameters may be partially due to cardiovascular reflexes rather than to mechanical factors alone. Vagal afferent reflexes may be present in the acute phase in both groups. On the other hand, the first day after the infarction, cardiac output, stroke volume, and dP/dt were more significantly depressed in the control group than in the methysergide pretreated group. Vagal afferent reflexes probably had less of a dampening effect on circulatory parameters at this time and the mechanical factors (the extent of myocardial injury) determined more accurately the degree of hemodynamic changes. By the eighth day all hemodynamic variables in both groups returned essentially to baseline.

There was a significantly greater increase in 5-HT levels in the coronary venous blood samples in the control group at the fifth hour when compared to the pretreated group. This would suggest that there was a larger amount of accumulated 5-HT that washed out from the affected area in the control group. This may support the assumption that blocking of 5-HT by methysergide protects the ischemic myocardium by reducing its vasoconstrictor effect on the microvasculature. This would reduce the probability of microthrombus formation and, therefore, a lower 5-HT level would be found in the ischemic affluency

The histological studies were inconclusive during the first five hours. This is not surprising since anatomical and histological evidence of myocardial necrosis is usually minimal in humans as well as dogs in these early stages of myocardial infarction. However in the animals followed for eight days, the evidence and extent of infarction was significantly less in the methysergide

pretreated hearts when compared to the control group. The histological findings correlated with the ECG results, with respect to the ΣQ wave amplitudes calculated over the 14 electrode sites. The ΣQ wave amplitudes in the methysergide group were significantly less ($p < 0.05$) than in the control group at the eighth day following LAD occlusion. This finding also supports our conclusion that methysergide pretreatment significantly protected the ischemic myocardium.

In this study the thrombus architecture produced by the helical wire was similar to the type which occurs naturally; that is, primarily platelets, fibrin, and associated leukocytic invasion. The essential difference between the naturally occurring thrombus and the one produced by this model was the initial site of platelet adherence, aggregation, and ultimate growth of the thrombus itself. In the former, of course, thrombus initiation is thought to develop at a discontinuous point in the endothelial lining, probably from a rupture of a sclerotic plaque. In the latter, the thrombus formed directly on the wire which was in intimate contact with the vessel wall.

The release of 5-HT from a venous thrombus is probably less critical on the whole as compared to the same process occurring on the arterial side of the general circulation, particularly in an artery directly leading to or within a vital organ system such as the heart. An occluding arterial thrombus may result in complete cessation of blood flow [illegible] to the obstruction, resulting in the ultimate [illegible]arction of tissue supplied by the vessel in question. A primary thrombus within a coronary artery releasing 5-HT will lead to concentration of this amine in the affected myocardial tissue. In contrast, 5-HT released by a venous thrombus or clot, is released directly into the venous return, diluted in the general circulation, and the over all effect is therefore minimized. The arterial thrombus is generally of the white thrombus type and is rich in platelets. In the red thrombus type that usually forms in the veins, platelets constitute a smaller percentage of the coagulum. Though specific studies dealing with the platelet release phenomenon were not investigated in this study, it can be reasonably assumed that our model produced the same in vivo coagulation mechanism and arterial thrombus having the characteristics of the one occurring naturally. We think that the factor initiating the first stage of the coagulation process on the wire is probably the same electrostatic mechanism which is thought to exist between platelets and cell fragments of a disrupted endothelial lining.

The mean platelet count in dogs[20] is approximately 300 × 10³ per mm. and in man it is about 250 × 10³ per mm. These reported values are an average for the two species but vary widely. In dogs,[21] platelets are small (3μ) azurophilic granules which are poor in histamine but contain concentrations of 5-HT varying between 0.25 μg per ml. of whole blood or 1.7μg per billion platelets. In man,[22] one ml. of whole blood is reported to average 0.10 μg of 5-HT or 0.3 to 0.5 μg per one billion platelets. The dog, therefore, has on the average, at least two and one half times as much 5-HT per ml. of whole blood and four times the concentration per billion platelets than that found in man. The dog appears to have, under normal circumstances, more circulating platelets (and 5-HT) per mm. than are found in man. However, there are physiological responses and certain conditions which significantly increase the number of circulating platelets. For example, the ingestion of specific foods over a period of several days[23] can increase circulating platelet serotonin concentrations from 2.5 to 6 times. Sequestered platelets, or platelet "pools," are primarily located in the lungs, spleen, and capillaries.[24] Mobilization of these granules may occur promptly under the influence of surgical or psychological stress,[25] under the mediation leading to catecholamines released, and during sympathetic neural stimulation. Not only is a thrombocytosis precipitated by these factors, but an increase in platelet adhesiveness is often associated with these phenomena. Serum lipemia following physical stress or smoking, for example, is another factor known to affect platelet adhesiveness.[26] The state of blood coagulability in brief is affected by numerous internal physiological as well as psychological stress factors. Since a thrombus is histologically composed primarily of platelets, fibrin, and a few trapped red blood cells, it would appear that the dog would have significantly more 5-HT available than man during an intracoronary thrombotic episode. It is conceivable, though, that given a set of psychophysiological stress conditions, the number of platelets and 5-HT concentration per ml. of human blood could reach those levels found in dogs. This then would parallel the condition found in this study regard

ing the concentration of 5-HT available at the time of thrombus formation.

The average total whole blood volume in the dogs used in these experiments ranged between two and three liters. There is, as stated above, approximately 0.25 μg of 5-HT per ml. in dog whole blood so the total concentration of expected endogenous platelet serotonin in these animals was approximately 500 to 700 μg. As one μg of methysergide will block ±10 μg of 5-HT 100 μg of methysergide per kilogram of body weight in each dog would be sufficient to combine with any amount of serotonin released during the development of an intracoronary thrombus.

The bradycardia and hypotension demonstrated during acute myocardial infarction, which was significantly less in the methysergide group than in the control group was probably reflex[17, 18] in nature. Zakusov[19] and Pidevich[20] found that the coronary chemoreflex could be elicited by 5-HT as well as by veratrine (nicotine) and could be suppressed by chlorpromazine. The reflex apnea, bradycardia, and hypotension demonstrated by Jacobs and Comroe[21] in cats after stimulating receptors in the nodose ganglion with 5-HT also supports the response of this compound on sensory organs. This general hemodynamic inhibitory effect by serotonin with respect to neural responses appears to be consistent in the literature. Local release of norepinephrine into coronary sinus blood has been demonstrated following 5-HT infusion directly into the LAD. Ascanio and associates[22] reported that the initial increase in dP/dt at the time of infarction is due to locally released tissue catecholamines from the myocardium, which they state are totally depleted approximately one hour following infarction.[23] This might be another explanation of the hemodynamic changes found in our study.

This results from this study support the hypothesis that at least one of the factors involved in acute myocardial failure during acute myocardial infarction is the release of 5-HT from the platelets involved in the thrombotic process. This may be due to the mediated release of norepinephrine, contributing to the negative inotropic response as well as to a decrease in neurogenic tone in the affected area. The assumed accumulation of 5-HT in the involved myocardium then may affect a severe small vessel vasoconstriction.

Whether or not methysergide will have a protective effect in early human myocardial infarction remains to be investigated. If it could be demonstrated in humans also that methysergide reduces the typical ischemic sequence to myocardial infarction, this drug could be used as an ancillary prophylactic measure in the medical management of high-risk patients with impending myocardial infarction and possibly for those surgical candidates undergoing coronary bypass procedures. It should be kept in mind however that certain fibrotic changes have been reported (Sandoz Pharmaceuticals) with long term, uninterrupted use of methysergide for up to six months, or longer. For this reason, the clinical application of this drug should probably be confined to short term use in the acute stages of an anticipated or precipitating thrombotic episode. The question remains as to what effect post-coronary occlusion treatment with methysergide would have on acute or chronic experimental myocardial ischemic states. We are presently conducting experiments in an attempt to answer this question.

Summary

The protective effect of methysergide on accumulating serotonin within the myocardium, during acute and chronic coronary thrombosis was evaluated in two groups of dogs. The first group of 15 dogs was pretreated with methysergide (100 μg/Kg. B.W. intravenously) and an equal number of dogs in the second group served as the control. An occluding intracoronary thrombus was produced in each dog by the closed chest placement of a thrombogenic wire into the left anterior descending (LAD) coronary artery via catheter technique, under x ray visualization. Blood pressure (BP) heart rate (HR), cardiac output (CO) stroke volume (SV), total peripheral resistance (TPR) and contractile force (dP/dt) were determined before and at 1, 3, and 5 hours (acute phase) after the onset of thrombosis. These variables were measured again at 1 and 8 days (chronic phase) after verified occlusion. The sums of the mean Q wave (ΣQ) and S-T segment (ΣS-T) amplitudes from 14 ECG precordial mapping sites were also calculated in six dogs of each group at these chronic time periods. Several biochemical variables were measured in the active phase from coronary venous blood specimens collected through the fifth hour. Histological examinations were also performed in the acute

and chronic phases on control and pretreated hearts. During the aforementioned sampling times certain hemodynamic variables decreased significantly ($p < 0.05$) in the control dogs, but less significant changes were found in the methysergide pretreated animals. There were similar differences in the mean concentration of certain biochemical variables between the two groups, in the acute stages of thrombosis, with less significant changes in the methysergide pretreated dogs. Generally there were less necrotic changes in the methysergide hearts at the eighth day but histological differences between the two groups were inconclusive in the acute phase. It appears from this study that the cardiodynamic and biochemical integrity was sustained by blocking the action of serotonin within the affected myocardium during myocardial infarction due to thrombotic occlusion of the LAD coronary artery.

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Effect of isoproterenol on regional myocardial perfusion and tissue oxygenation in acute myocardial infarction

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It is well established that the beta adrenergic agonist isoproterenol enhances cardiac performance by increasing cardiac output and myocardial contractile force in both normal and acutely infarcted hearts. However these changes are accomplished at the cost of an increase in myocardial oxygen consumption. In normal hearts, the increase in local myocardial oxygen requirements is usually compensated for by an appropriate increase in coronary blood flow However the capacity of an abnormal coronary vascular bed to meet increased oxygen demands due to sympathetic stimulation has not been clear If an adverse effect of isoproterenol upon the balance between myocardial oxygen supply and demand should increase ischemia in the *region immediately surrounding infarcted tissue*, the value of this drug for therapy of complications of acute myocardial infarction would be doubtful, despite its ameliorative effects on cardiac performance.

To investigate the possibility that isoproterenol could have opposing effects on local tissue oxygenation and over-all cardiac function we utilized a canine model of acute myocardial infarction. Regional myocardial perfusion was measured with radioactive microspheres and the adequacy of tissue oxygenation was estimated by analysis of myocardial biopsies for lactate and adenosine triphosphate (ATP)

Methods

Under alpha-chloralose anesthesia, left thoracotomies were performed in 20 mongrel dogs weighing 10 to 24 kilograms. A calibrated electromagnetic flow probe was placed around the ascending aorta and 18 gauge polyethylene catheters were inserted into the left atrium and the left carotid artery A silk suture was placed around a large diagonal branch of the left anterior descending coronary artery The open-chested animal remained under anesthesia during the *entire study- duration of the study was less than* 1.5 hours.

Aortic phasic flow was obtained with a Zepeda square wave electromagnetic flowmeter It was assumed that flow was zero at end diastole. Stroke volume was obtained by integrating the systolic portion of the phasic flow signal with an active resistance–capacitance network. The mean left atrial pressure was measured via the implanted catheter by a Statham P23Db manometer the arterial pressure was measured by a similar method via the left carotid *catheter*

Regional coronary blood flow was determined utilizing the radioactive microsphere technique. Three separate radioactive labels, [illegible]Sr [illegible]Sc, and Ce in inert spheres measuring 10 to 20 microns were used. A bolus of spheres with one of these labels was injected into the left atrium during each of three measurement points. At the termination of the experiment, the animal was

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Table I Hemodynamic values in 13 experimental and seven control dogs

		Control	*p Infarct*	*Isoproterenol*
A. Isoproterenol (n = 13)				
HR	$\bar{x}$	155 ± 7	154 ± 7	204 ± 9
(beats/min.)	$\bar{d}$			50.6 ± 6.3
	p			<0.001
CO	$\bar{x}$	2.63 ± 0.40	2.30 ± 0.31	2.83 ± 0.44
(min.)	$\bar{d}$			0.53 ± 0.19
	p			<0.01
$\bar{x}$ AOP	$\bar{x}$	86 ± 6	82 ± 6	60 ± 8
(mm. Hg)	$\bar{d}$			21.6 ± 4.8
	p			<0.01
TPR	$\bar{x}$	37 ± 6	28 ± 5	26 ± 6
(P.R.U.)	$\bar{d}$			11.9 ± 2.8
	p			<0.01

		Control	*p Infarct*	*Saline*
B. Saline controls (n = 7)				
HR	$\bar{x}$	158 ± 15	168 ± 15	166 ± 14
(beats/min.)	$\bar{d}$			2.3 ± 2.2
	p			N.S.
CO	$\bar{x}$	3.07 ± 0.44	2.86 ± 0.38	2.48 ± 0.28
(L./min.)	$\bar{d}$			0.38 ± 0.17
	p			N.S.
$\bar{x}$ AOP	$\bar{x}$	83 ± 8	80 ± 9	78 ± 7
	$\bar{d}$			2.3 ± 2.7
	p			N.S.
TPR	$\bar{x}$	31 ± 4	30 ± 4	33 ± 5
	$\bar{d}$			3.1 ± 2.8
	p			N.S.

$\bar{x}$ = mean absolute value ± standard error $\bar{d}$ = mean difference ± standard error of the difference p = p value by paired comparison of p infarct and isoproterenol results; N.S. = p ≥ 0.05, HR = heart rate, CO = cardiac output, $\bar{x}$ AOP = mean aortic pressure, TPR = total peripheral resistance in peripheral resistance units. CO and TPR were not measured in one dog in the isoproterenol and one dog in the control groups.

killed and myocardial tissue samples were obtained. Two, approximately 1 cm diameter transmural samples were obtained from each region of interest and counted in a well-type scintillation counter. Each sample contained at least 500 microspheres.

Tissue lactate and ATP values were determined from 1 mg. tissue samples obtained by Vim-Silverman needle transmural biopsies. Fluorometric assays were used.

The animals were divided into two groups. Group A consisted of 10 dogs continuously infused with isoproterenol at a rate of 0.15 μg/Kg./minute for 10 minutes and Group B consisted of seven dogs infused with an equal volume of saline as a control. Cardiac output, mean aortic pressure, heart rate, and electrocardiograms were monitored continuously throughout the experiment. Hemodynamic and regional flow measurements were made at three points during the experiment: the initial measurement made prior to coronary occlusion, the second 15 minutes after occlusion just prior to infusion, and the third made immediately after the infusion.

Three separate regions were identified on the myocardial surface. One, on the lateral aspect of the left ventricle, where vascular supply was intact, was termed the "normal" region. The second, just distal to the tie, was grossly cyanotic and edematous and was termed the "infarct" region. The third region surrounded the infarct, was slightly discolored but did not appear to be necrotic, and was termed the "marginal" area. The presence of an infarct was confirmed *in vivo* by visualization and by electrocardiographic changes. In several dogs the infarct was also confirmed by either fluorescent dye or ECG mapping. Biopsies for myocardial lactate and ATP were obtained from each region *in vivo* during the post ligation and infusion periods. A statistical analysis was done using paired comparisons with the Student t test.

Results

The hemodynamic changes with isoproterenol infusion are shown in Table I. Heart rate increased by 51 beats/minute (+33 per cent), cardiac output increased by 0.53 L/minute (+23 per cent), aortic pressure fell by 22 mm. Hg (−26 per cent), and total peripheral resistance fell by 12 P.R.U. (−31 per cent). No consistent or significant changes occurred when saline was infused in the control dogs.

Results of regional myocardial flow measurements are shown in Table II. Prior to ligation of the left anterior descending coronary artery there were no significant differences in flow among the various regions studied in either the experimental or the control group. After ligation in the experimental group, flow was not significantly altered in the normal region but decreased by 11 per cent in the marginal and by 52 per cent in the infarct regions; similar changes occurred in the control group. During isoproterenol infusion, in eight of 12 dogs, flow increased in the normal regions but this increase from a mean of 74 mL/100 g/minute to 83 mL/100 g/minute was not statistically significant. There was no tendency for flows to

Table II Regional myocardial flow (ml./100 g/min.)

	Normal region	*Marginal region*	*Infarct region*
Experimental group (n = 12)			
Pre-infarct	61 ± 6	57 ± 6	56 ± 6
Post-infarct	4 ± 10	51 ± 6	27 ± 4
Isoproterenol	93 ± 17	59 ± 12	26 ± 9
Control group (n = 6)			
Pre-infarct	62 ± 24	72 ± 20	77 ± 27
Post-infarct	76 ± 17	68 ± 14	44 ± 8
Saline	86 ± 16	56 ± 13	44 ± 6

Flows expressed as mean   standard error in 12 experimental and six control dogs. There were no significant changes due to isoproterenol or saline although 8 of 12 dogs had increased flows in the normal regions with isoproterenol.

change with isoproterenol in the marginal and infarct regions. There were no changes in regional myocardial flow when saline was administered to the control group.

Changes in regional myocardial lactate concentration are shown in Table III After ligation of the coronary artery before isoproterenol infusion mean lactate concentrations expressed per gram of wet tissue were 3.6 ± 0.3 (s.e.) μmols/g in the normal region, 5.8 ± 1.0 in the marginal region, and 8.9 ± 0.9 in the infarct region. During isoproterenol there was a doubling of the lactate level in the marginal region (+5 6 μmols/g, $P < 0.05$) There were no significant changes in the normal or infarct regions, although some dogs had substantial increases in the infarcted tissue. Lactates in five control dogs did not change in any consistent manner with isoproterenol infusion.

Results of regional myocardial ATP measurements are shown in Table IV Post ligation but prior to isoproterenol, infusion values were 7.1 ± 1.1 μmols/g in the normal region, 5.2 ± 0.9 μmols/g in the marginal region, and 3.1 μmols/g in the infarct region The only significant change with isoproterenol was a 46 per cent decline in ATP concentration in the marginal regions (−2.4 μmols/g, $p < 0.05$) No consistent changes occurred in the control dogs.

Discussion

When myocardial tissue is inadequately supplied with oxygen, lactate tends to accumulate and energy sources are depleted. Therefore, the increase in lactate and decrease in ATP in biop-

Table III Myocardial lactate concentrations (mols/g)

	Normal region	*Marginal region*	*Infarct region*
A. Experimental group (n = 10)			
Post-infarct	3.6 ± 0.3	5.8 ± 1.0	8.9 ± 0.9
Isoproterenol	4.7 ± 0.7	11.4 ± 2.3	11.5 ± 1.6
B. Control group (n = 5)			
Post-infarct	2.9 ± 0.4	4.5 ± 0.9	6.1 ± 1.2
Saline	2.7 ± 0.7	3.5 ± 0.6	7.9 ± 0.6

Lactate per gram of wet tissue in 10 dogs infused with isoproterenol and 5 dogs infused with saline. Values are mean ± standard error. * = $p < 0.05$ for paired comparison of post-infarct and isoproterenol values. In the control group infarct values were obtained in only four dogs because of   technical problem.

Table IV Myocardial ATP concentrations (mols/g)

	Normal region	*Marginal region*	*Infarct region*
A. Experimental group (n = 8)			
Post-infarct	7.1 ± 1.1	5.2 ± 0.9	3.1 ± 0.3
Isoproterenol	4.8 ± 0.9	2.8 ± 0.6*	2.8 ± 0.6
B. Control group (n = 5)			
Post-infarct	8.0 ± 0.6	6.4 ± 1.3	4.1 ± 0.7
Saline	6.5 ± 1.4	5.6 ± 1.4	4.3 ± 1.0

ATP values in eight dogs infused with isoproterenol and five dogs infused with saline. Symbols as in Table III. In the control group infarct values were obtained in only four dogs because of   technical problem.

sies from marginal tissue during isoproterenol infusion is evidence of exacerbation of regional hypoxia. If sustained, it is likely that the worsening ischemia would result in expansion of the infarct. The lack of change in the infarct regions may mean that biochemical disturbances due to hypoxia were already near maximal there, so that no further increments in lactate or decrements in ATP could occur

Both lactate and ATP levels were unchanged in the normal regions during isoproterenol infusions. It is likely therefore, that the tendency of this level of beta-adrenergic stimulation to create hypoxia was limited to regions where ligation of a coronary artery interfered with myocardial perfusion. Myocardial perfusion was markedly reduced in the marginal and infarct regions after coronary ligation and showed no tendency to increase during isoproterenol. Flows in the normal regions were considerably higher and in most dogs increased with isoproterenol. It is not clear why

flow did not increase in normal regions with isoproterenol in some dogs perhaps marked reduction in aortic pressure limited increases in myocardial oxygen need.

Increased ischemic changes in unipolar electrocardiographic leads over marginal regions due to isoproterenol have been reported.[2] Our direct measurements of biochemical correlates of ischemia are in agreement with these electrocardiographic data. Thus it would appear that levels of beta-adrenergic stimulation which improve cardiac performance but are below levels which cause diffuse necrosis in normal hearts will worsen ischemia in acute myocardial infarction. If this data in a canine model can be extrapolated to the clinical setting, it could be questioned whether use of isoproterenol to correct low cardiac output in acute myocardial infarction is advisable. Because of the danger of extension of infarcts with isoproterenol, other modes of therapy may be superior In addition, since beta stimulation with isoproterenol is to some extent analogous to endogenous catecholamine stimulation, the possibility that emotional stress or increased physical activity may have similar adverse effects on myocardial oxygenation in acute myocardial infarction must be considered.

Summary

The effect of isoproterenol infusion on regional myocardial perfusion and tissue oxygenation in acute myocardial infarction was investigated in anesthetized dogs. Measurements of regional flow with radioactive microspheres and myocardial lactate and adenosine triphosphate from analysis of myocardial biopsies were compared in normal, marginal, and infarcted tissue in dogs with a ligated coronary artery After 10 minutes of isoproterenol 0 15 μg/Kg./minute, flow was unchanged in the marginal and infarcted regions, and, although rises occurred in most dogs, changes were inconsistent in the normal regions. In the marginal regions, tissue lactate rose by 5.6 μmoles/g (97 per cent) and adenosine triphosphate fell by 2.4 μmoles/g (46 per cent) after isoproterenol. No consistent changes occurred in the normal or infarcted regions of the dogs given isoproterenol or in any regions of control dogs given saline. It is concluded that beta-adrenergic stimulation with isoproterenol increases tissue ischemia in experimental acute myocardial infarction.

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Effect of isoproterenol on the early repolarization syndrome

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In 1936 Shipley and Hallaran first described RS-T segment elevation mimicking cardiac disease in apparently normal persons. This electrocardiographic pattern is characterized by a concave up RS-T segment elevation in the anterolateral precordial leads and/or inferior limb leads. The degree of elevation does not usually exceed 0.4 mv Tall peaked T waves are often seen in association with RS-T segment elevation while negative precordial T waves constitute a very unusual finding. This normal variant of RS-T elevation is commonly termed early repolarization syndrome. It is found in about 2 per cent of healthy adults and is more commonly encountered in young black subjects. A similar electrocardiographic pattern is observed in the so-called "vagotonia."

From a practical point of view the interest of these patterns lies in the fact that sometimes they closely mimic acute pericarditis, hyperkalemia, or an epicardial injury current.

In order to investigate the electrophysiological basis of the normal variant of RS-T segment elevation we have evaluated the effects of different drugs and of exercise on a group of normal subjects presenting with this syndrome.

Material and methods

The study group consisted of 12 normal healthy subjects (10 males and two females) aged 26 to 71 years, presenting a concave upwards elevation (0.1 to 0.3 mv) of the RS-T segment in the anterolateral precordial leads in 11 cases and in the inferior limb leads in one case. One patient was referred to us for cardiologic evaluation after an epicardial injury had been suspected. The other patients were undergoing a routine ECG for the first time. Each patient was subjected to complete medical history and physical examination standard blood tests, chest x rays, and follow up electrocardiograms were also performed. All the patients showed normal tolerance to strain and in none of them was there evidence of heart disease. The ECG was recorded with a Mingograf 62 Siemens-Electra direct writing electrocardiograph. The ECG was recorded before and after the intravenous infusion of a solution containing 0.2 mg. of isoproterenol (ISP) in 100 c.c. of aqueous dextrose. The rate of infusion was adjusted so as to administer 4 mcg. of ISP in 1 minute. Infusion was discontinued when heart rate increased by 30 to 50 beats/minute or when ectopic beats appeared. The intravenous administration of propranolol (P) in the dose of 2 to 4 mg., followed ISP In some cases, P was not preceded by ISP As a control, atropine or amyl nitrite (AN) were administered on different

Patients were required to carry out phy

exercise (double two-steps M test)

The following parameters ev

RS-T segment, T wave, R R Q-T

Q-T intervals. The latter was

ing to Bazett s formula (Q-T

expressed as a per cent of the

Results

The effects that the intr

isoproterenol had on R R, Q-

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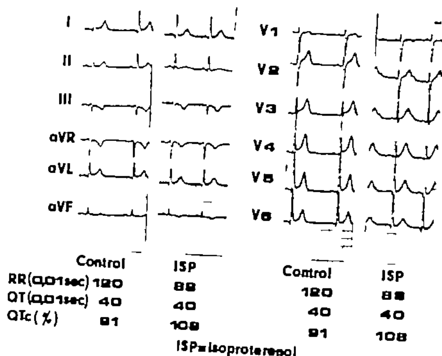


Fig. 1 Return to the isoelectric line of the ST segment during isoproterenol infusion.

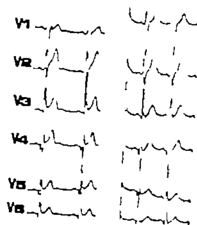


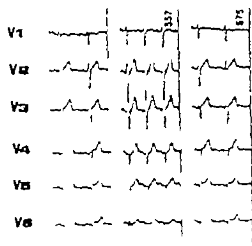
Fig. 2. The ST segment becomes isoelec nd he QT interval shortens during isoprot renol i

Table I Effects of isoproterenol on RR, QT and QT intervals

Patient No.	*RR(0.01 sec)*		*QT (0.01 sec.)*		*QT (%)*	
	C	*ISP*	*C*	*ISP*	*C*	*ISP*
1	120	68	40	36	92	116
2	100	72	38	38	96	107
3	80	48	34	32	96	116
4	108	68	38	34	87	104
5	106	76	38	36	92	103
6	120	88	40	40	91	108
7	124	68	38	36	88	110
8	88	44	36	32	97	121
9	84	44	36	32	96	121
10	80	52	32	32	90	111
11	76	52	32	32	92	111
12	104	64	40	38	99	119
Mean	98.5	62	36.6	34.6	92.6	111.7
SD	±16	±14	±3	±7	±4	±6.2

*Significant difference between control values and values after isoproterenol infusion ($P < 0.001$)

vals are reported in Table I In p t tl Q-T interval ranged from 86 per nt t 9 pe cent (mean 93 per cent) of the theore i l Following ISP administration the RS-T se m t was always lowered, becoming isoelectric slightly depressed in some cases. The T wave decreased in amplitude or became slurred or negative In nine of the 12 cases the Q T interval sh rtened, while in all the cases the Q-T interval lengthened (Figs. 1 and 2). Even after exercise the normalization of the RS-T segment and a decreased Q T interval were observed. Propranolol administration after ISP restored the upward



	Control	ISP	P
RR (0,01sec)	80	48	78
QT (0,01sec)	34	32	34
QTc (%)	85	116	88

ISP Isoproterenol
P= propranolol

Fig. 3. Isoproterenol produces lowering of the ST segment and shortens the QT interval, while propranolol exaggerates ST segment elevation.

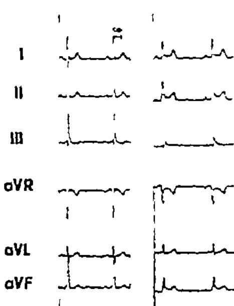
concave RS-T elevation (Fig. 3) When P administration was not preceded by ISP the RS-T elevation increased, without any change in the Q-T interval (Fig. 4)

In the case reported in Fig. 4, the RS-T segment elevation after P administration is higher in the limb leads than in the precordial leads. A notch or slur on the downstroke of the R wave can be seen. After P administration this patient also showed a sharp decrease in QRS voltage, while the P wave remained unchanged.

Atropine administration and inhalation of amyl-nitrite (Fig. 5) had no effect on either RS-T segment elevation, or Q-T interval, while Q-T increased.

Discussion

The effects of different drugs on the early repolarization syndrome were studied in order to test the functional nature of this RS-T segment elevation and the possible link between this syndrome and other primary T wave abnormalities affected by maneuvers or drugs acting via the autonomic nervous system. In all the cases ISP infusion was followed by the normalization of the RS-T segment and a reduction of the T wave



	control	P
RR (0,01sec)	104	112
QT (0 01sec)	34	34
QTc(%)	83	81

P = propranolol

Fig. 4 ST segment elevation following propranolol administration.

amplitude. These effects were not rate-dependent. The RS-T segment elevation remained unchanged when similar values of the heart rate were obtained by atropine administration or amyl-nitrite inhalation. On the other hand, the enhanced elevation observed after P administration was not always accompanied by bradycardia. While the normalization of the RS-T segment was associated with a shortening of the Q-T interval, the latter lengthened when the elevation of the RS-T segment increased. In the former case we observed a lengthening of the Q-T interval due to hysteresis related to the increase of the heart rate.

These results suggest that the concave elevation of the RS-T segment is in some way linked to the length of the Q-T interval. As the normalization induced by ISP does not seem due to the increase in the heart rate, the direct effect of the drug on myocardial fibers should explain the electrogenesis of the "early repolarization" syndrome. ISP produces the reversal of T wave

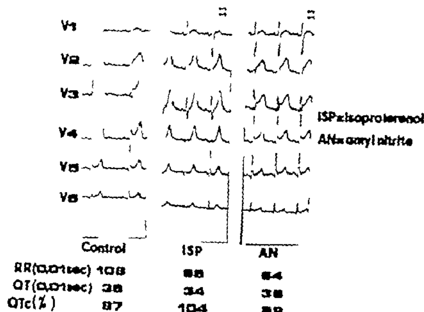


Fig 8 Isoproterenol produces lowering of the ST segment and shortens the QT interval, while amyl-nitrite does not change ST segment elevation.

polarity in some normal subjects and this effect has been referred to regional variations of ventricular action potential. The shortening of the action potential depends on resting conditions it is marked if the action potential is abnormally long, it is practically unapparent if the action potential is of normal duration. The upward concave elevation of the RS-T segment could be to an anomalous ventricular gradient between a site with faster recovery underlying the lead with RS-T segment elevation and a site with slower recovery most probably the postero-basal region of the heart, on which the effect of ISP seems to be exerted. The early repolarization of the apico-anterior wall may be related to an enhanced activity of the right sympathetic nerves, which mostly run to the interventricular septum and anterior wall of the heart Some experimental studies have demonstrated that the unilateral stimulation of the right recurrent nerve or of the right stellate ganglion induces an elevation of the RS-T segment which is quite similar to that recorded in patients with the early repolarization syndrome

Summary

A study has been carried ut on a group of subjects with RS-T segment l vation a normal variant of early rep lari at n F llowing isoproterenol administrati n the RS T segment became isoelectric. In most cases this was accompanied by shorter QT and longer QT intervals. The same effects were observed after physical exertion but not after atropine or amyl-nitrite. Propranolol administration exaggerated RS-T elevation.

Considering the mechanism with which isoproterenol acts and some analogies with the electrocardiographic picture experimentally obtained by means of the unilateral stimulation of the stellate ganglions, the hypothesis is advanced that the normal variant of early repolarization is related to an enhanced activity of the right sympathetic nerves.

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The effect of exercise on left ventricular ejection time in patients with hypertension or angina pectoris

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Abnormal prolongation of post-exercise left ventricular ejection time in patients with ischemic heart disease was first described by Pouget and colleagues in 1971. In a recent study confirming this finding, Lewis and associates[2] introduced a new regression equation for calculating a supine rate-corrected post-exercise value for the left ventricular ejection time and applied it to a group of patients with ischemic heart disease. The present study is an initial report of the effect of exercise on left ventricular ejection time in a group of hypertensive patients and also confirms the findings of Lewis and co-workers in a group of normal persons and in a group of patients with angina pectoris.

[illegible]aterial

Ninety five males between the ages of 35 and 65 years were studied. Fifty five men were considered to be normal and served as a control group. They were free of any sign or symptom suggesting organic heart disease and demonstrated a non ischemic electrocardiographic response to symptom limited maximal graded treadmill exercise. Twenty five patients with uncomplicated hypertension were evaluated. They denied angina pectoris and demonstrated a non ischemic electrocardiographic response to exercise. Fifteen patients with stable angina pectoris were also evaluated. They had n[illegible] hist[illegible] r[illegible] electr[illegible]cardiographic eviden[illegible] [illegible]f pri[illegible]r my[illegible]ocardial infarcti[illegible]n were normoten[illegible] and d[illegible] [illegible]ted an ischemic electrocardi[illegible]graphi[illegible] respon[illegible] [illegible] exercise.

A fourth group, a sub-group of 18 patients from the normal controls over 50 years of age, were evaluated separately as their mean age was similar to that of the patients with angina pectoris. None of the patients was receiving medication at the time of the test.

Method

A signed informed consent form was obtained, a hemoglobin level was determined, and the patients were questioned and examined for signs of recent changes in their cardiovascular status. The tests were performed in the post absorptive state. A resting supine electrocardiogram was recorded. Using a Cambridge FibreOptic Medical Recorder, a transducer with a time constant of greater than 3.2 seconds, and a paper speed of 100 mm./second, supine systolic time intervals were recorded using the average of ten cardiac cycles as the basis for calculation. Precordial electrodes were placed in the C-C position: the positive electrode was placed in the left V position, the negative electrode was placed in the right V position, and the ground electrode was positioned in the right infraclavicular area. A stethoscope and sphygmomanometer were affixed to the right arm. Pre-exercise heart rate, blood pressure, and C-C electrocardiogram were recorded in the supine and standing positions and following a period of hyperventilation. Using the Bruce protocol, exercise was continued until symptom limited fatigue, incoordination, angina pectoris, or falling systolic blood pressure precluded further effort. The C-C electrocardiogram was monitored throughout and recordings of heart rate, blood pressure, and electrocardiogram were made at 90 second intervals. Following exercise the patients resumed the supine position for

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Table I Results of the effect of exercise on the double product and left ventricular ejection time

		Normal	*Hypertensive*	*Angina*	*Normal, 50+ yrs*
Total patients		55	25	15	16
Age in years		47.0 ± 1.0	47.5 ± 1.2	55.0 ± 1.5	55.9 ± 1.1
Double product (heart rate × systolic blood pressure × 10⁻)					
Supine		80 ± 2	115 ± 6*	86 ± 4	79 ± 4
Standing		93 ± 3	135 ± 7	103 ± 7	90 ± 4
Stage I†	3 min.	173 ± 4	230 ± 11	196 ± 10*	162 ± 6
Stage II	3 min.	204 ± 5	313 ± 11	246 ± 12 (13)	227 ± 8
Stage III	3 min.	280 ± 6 (49)	365 ± 12 (21)	223 ± 26* (4)	291 ± 13 (15)
Stage IV	1½ min.	295 ± 8 (24)	401 ± 23* (7)	–	289 ± 16 (6)
Recovery	4 min.	133 ± 2	157 ± 7*	116 ± 8*	125 ± 4
Heart rate/minute and Deviation of left ventricular ejection time (ΔLVET) in milliseconds					
Pre-exercise					
Heart rate		66.0 ± 1.4	75.3 ± 2.6*	65.7 ± 2.1	65.9 ± 2.4
ΔLVET (mean 413)		−8.2 ± 1.8	−14.1 ± 2.9	−15.4 ± 2.7	−7.3 ± 3.2
Post-exercise					
Heart rate		102.3 ± 1.8	110.8 ± 2.5	82.8 ± 4.8*	94.8 ± 3.3
ΔLVET (mean 371)		+3.0 ± 1.8	−2.3 ± 2.3	+11.1 ± 2.5	+3.4 ± 2.8
Net deviation of left ventricular ejection time (net ΔLVET)		+11.2 ± 2.0	+11.8 ± 2.3	+26.5 ± 4.5	+10.8 ± 3.4

Values are expressed as the mean ± standard error of the mean.
† = Bruce protocol.
Numbers in parentheses = Patients completing that stage of exercise
* = $P < .05$.
** = $P < .01$.
*** = $P < .001$ All P values are compared to the normal subjects ($N = 55$)

monitoring during recovery Supine systolic time intervals were again recorded at 4 minutes of recovery

Definitions and calculations

An ischemic electrocardiographic response was considered to be present if the ST-segment was horizontal or downsloping with a 1 mm. or greater depression at a point 80 msec. following the nadir of the S-wave. The double product (DP) of heart rate times systolic blood pressure ($HR \times SBP \times 10^{-}$) was calculated for each level of exercise and at 4 minutes of recovery

Using the resting supine regression equation of Weissler and colleagues, and expressing the results in milliseconds, the pre-exercise rate corrected left ventricular ejection time index (LVETI) was calculated

$$LVETI = (1.7 \times HR) + LVET$$

The deviation of left ventricular ejection time index from the mean was calculated

$$\text{pre-exercise } \Delta LVETI = LVETI - 413$$

The post-exercise regression equation of Lewis and colleagues was used to calculate the rate-corrected post-exercise left ventricular ejection time index

$$LVETI = (1.32 \times HR) + LVET$$

The deviation from the mean (ΔLVETI) was calculated

$$\text{post-exercise } \Delta LVETI = LVETI - 371$$

The net change in the left ventricular ejection time (net ΔLVET) was calculated.

$$\text{net } \Delta LVET = \text{post } \Delta LVETI - \text{pre } \Delta LVETI$$

Results

The results are summarized in Table I and are expressed as the mean ± standard error of the mean. The P values were determined by using the two-tailed t test of significance.

The mean ages of the normal patients (47.0 ± 1.0) and the hypertensive patients (47.5 ± 1.2) were similar The mean age of the anginal patients (55.0 ± 1.5) was significantly higher than the control group ($P < .001$) The mean age of the sub-group of normals age 50 and older (55.0 ± 1.1) was similar to the anginal patients ($P < .001$).

The double product (DP) an indirect measure of cardiac work, was significantly higher in the hypertensive patients at each level of exercise ($P < .001$) Initially the normal and anginal patients had similar double products. However

there was a slight fall of the double product in the anginal patients during the final phases of exercise and in recovery ($P < .01$). This was also observed at 4 minutes of recovery in the subgroup of normals over 50 years of age ($P < .01$)

The pre-exercise ΔLVET values were similar in all groups. At 4 minutes of recovery the post exercise ΔLVET was slightly prolonged in the anginal patients ($P < .05$) The net ΔLVET however was significantly prolonged in the patients with angina pectoris ($P < .001$) This was not observed in the hypertensive group or in the normals over 50 years of age. The net change in the left ventricular ejection time (net ΔLVET) in msec. are as follows Normal = $+11.3 \pm 2.0$ Hypertensive = $+11.8 \pm 2.3$ Anginal patients = $+26.5 \pm 4.5$ Normal 50 + years = $+10.8 \pm 3.4$.

Discussion

As exercise testing has become more widely available for evaluating cardiovascular function, there have been increasing attempts to quantitate the results obtained with the degree of coronary artery disease that may be present. Utilizing electrocardiographic criteria alone this has not been entirely satisfactory For this reason additional parameters are being evaulated to obtain a more accurate assessment of cardiac function and the extent of coronary artery disease.

Studying patients with angina pectoris, Pouget [1] colleagues found an abnormal prolongation post-exercise left ventricular ejection time when compared to normals. Cardus and Vera, in 1974 reported on the effect of exercise on systolic time intervals in normal subjects and presented regression equations for rate-correction in the upright position. Miller and Bahler[8] have also reported on the prolongation of left ventricular ejection time following exercise in patients with latent ischemic heart disease Lewis, and associates, in their recent study utilizing a graded treadmill protocol, measured supine left ventricular ejection time before and after exercise, and using separate regression equations to correct the values for heart rate, found a mean increase of 11 msec. in the control group with an upper normal limit of 31 msec. Fifty patients with coronary artery disease showed a mean increase of 31 msec. and 11 of these 50 patients (22 per cent) were abnormally prolonged. In the present study five normal subjects had values above 31 msec., none of the hypertensive patients showed an abnormal prolongation, and five of the 15 anginal patients (33 per cent) showed values above 31 msec.

Summary

Using the method and regression equation of Lewis and associates, the present study confirms their findings in normal men up to the age of 65 years. Despite the significantly higher myocardial oxygen consumption, as measured by the double product, the hypertensive patients responded in a similar fashion The patients with angina pectoris, however showed a significantly prolonged post-exercise ejection time.

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Ventricular tachycardia produced by hyperosmotic solutions injected into the left main coronary artery in dogs

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Carson and Lazzara revealed that sinus slowing can be produced by intracoronary injection of hyperosmotic solutions in anesthetized dogs. More recently this finding has also been confirmed in the human heart by the author and his associates. Although postcapillary venules were assumed as the site of osmotic action, it has not been clarified in previous studies. As the first step for detecting its localization, it was examined in this laboratory whether the site might exist in the left main coronary artery (LMC) injection of hyperosmotic solution into the LMC of the canine hearts, where the LMC was "isolated" from the left anterior descending (LAD) and the left circumflex (LCX) coronary arteries by aorto(Ao)-coronary bypass grafting, was carried out. No osmotically induced sinus slowing, however could be observed in this experiment, and ventricular tachycardia (VT) instead, was noted to be evoked in all dogs studied.

It is the object of this paper to describe the characteristics of the VT thus evoked and discuss its genesis.

Methods

Twenty-six mongrel dogs, weighing between 20 and 42 kilograms (average 27.2 Kg) were anesthetized with intramuscular pentobarbital sodium (35 mg. per kilogram), intubated with a cuffed endotracheal tube, and ventilated with 40 per cent oxygen-mixed room air using a Harvard

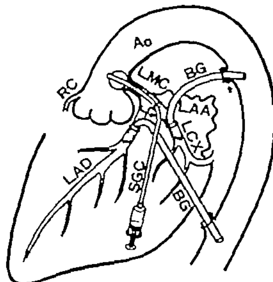


Fig. 1 Schematic representation of the experimental design. The LAD and LCX are ligated just below the bifurcation, and the distributions of the LAD and LCX are supplied blood through the bypass grafts from the descending Ao. An SGC was introduced from the proximal LCX, of which the tip reached the lumen of the ascending Ao. At each injection the balloon was inflated and the catheter was slightly pulled backward for ostial occlusion. Injected fluid was poured through the side-holes of the SGC into the lumen of the LMC. Abbreviations: *Ao* = aorta, *BG* = bypass graft, *LAA* = left atrial appendage (*retracted here*); *LAD* = left anterior descending coronary artery; *LCX* = left circumflex coronary artery; *LMC* = left main coronary artery; *RC* = right coronary artery; *SGC* = Swan-Ganz catheter. *Arrows* = ligation.

respirator. Subcutaneous electrodes were placed in the limbs to monitor a Lead II electrocardiogram (ECG). Bilateral thoracotomy was performed at the second and fourth interspaces. Bilateral stellate ganglia, all their pre- and postganglionic fibers, the sympathetic ganglia from T

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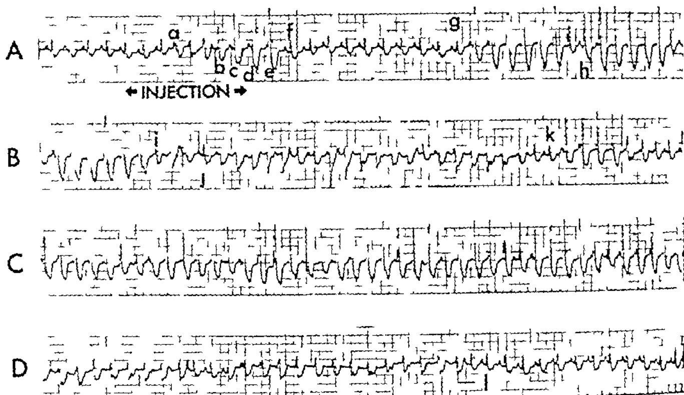


Fig 2. Ventricular tachycardia (VT) produced by an injection of 30 per cent saline into the left main coronary artery (LMC) showing beginning and ending of paroxysm of VT A Heart rat was 135 beats per minute before injection Ectopic beats of entricular origin started t the beat marked a. The contraction "b was fusion beat, followed by more widened QRS complexes t e where A V dissociation was apparent, trial rate 135 per minute, entricular more than 150. Transient resumption of normal sinus rhythm (beats "f" to g") followed by paroxysm of VT with regular rate Contraction marked "h was fusion beat. B, Successive record. Beats ("i to k) having miscellaneous QRS configuration and regular R R intervals (0.38 sec.), followed the preceding common type of VT where also A V dissociation was evidently observed, atrial rate 130 per minute, entricular 156 The beats j and k were ventricular captures. Polarity was mainly negative here. C, 40 seconds after the injection D Eight minutes after injection Spontaneous termination of VT A V dissociation was observed, where the polarity was biphasic mainly before the first beat l of the restored normal sinus rhythm.

to T and their preganglionic fibers were identi fied. Two polyvinyl tubes (inside diameter 2.2 mm., outside diameter 3 5 mm) were cannulated into the descending thoracic Ao with a distance of several cm The heart was cradled in the opened pericardium incised parallel to the phrenic nerve. The LAD and the LCX were exposed just below the bifurcation After ligation of the rigin of the LAD Ao-LAD bypass was made ju t below the bifurcation using one of the tubes alr ady annu lated into the descending Ao whi l wa f ll wed by Ao-LCX bypass grafting with th ot annu la. The tip of a Swan (n ath 8 F) was introduced from th rign f h (to the ascending Ao b as t th LMC l balloon of the catheter w nfl t n the ascending Ao and the catheter was drawn back slightly to occlude the left coronary ostium with the balloon. The LCX was constricted by a ligature with the inserted catheter at its origin (Fig. 1)

Injections were performed during sinus rhythm at a speed of 0.5 ml. per second into the LMC utilizing a 1.5 ml. quantity of distilled water hydroxyethyl starch, normal saline, 20 per cent mannitol, 76 per cent Urografin, 10 per cent sodium bicarbonate, 50 per cent glucose 10 per cent and 30 per cent saline. Osmolality and pH of these solutions are shown in Table I After each injection the balloon of the catheter was deflated and repeated wash-out of the lumen of the catheter and that of the LMC were performed with

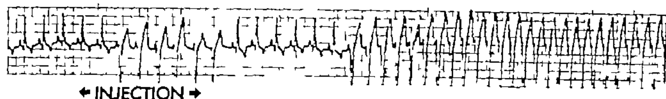


Fig. 3. VT produced by 50 per cent glucose solution injected into the LMC.

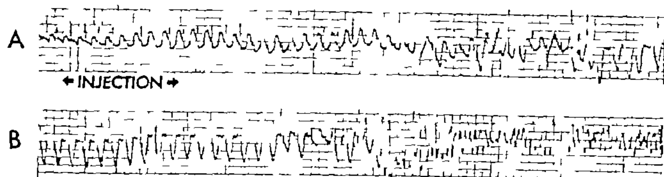


Fig. 4. VT elicited by 10 per cent sodium bicarbonate solution and transition of the VT to ventricular fibrillation. *A*, VT starting as ventricular rhythm irregular both in rate and in QRS configuration. *B*, Successive record. VT with regular ventricular rate, followed by suddenly increased ventricular rate resulting in the transition to ventricular fibrillation.

arterial blood. ECG was recorded before, during, and after each injection until cessation of VT if evoked, and, if not, an ECG tracing was done for 30 seconds from the initiation of injection.

To investigate whether an autonomic system of the hearts consisting of extrinsic (sympathetic and vagus nerves) and "intrinsic" innervation might be responsible for the genesis of the VT or not, ECG's were also traced with injection under cardiac denervation. The means for denervation were the following: (1) bilateral vagotomy at the cervical or thoracic level, (2) cardiac sympathetic denervation, consisting of bilateral stellectomy and T to T sympathetic ganglionectomy (3) bilateral vagotomy and cardiac sympathetic denervation (classic total cardiac denervation) (4) propranolol administration (propranolol, 0.6 mg. per kilogram, intravenously) following classic total cardiac denervation, or (5) atropinization (atropine, 0.15 mg. per kilogram, intravenously) in addition to classic total cardiac denervation and propranolol administration.

In another series of supplemental experiments (while under bypass grafting) ECG's were traced in the following conditions (1) the left coronary ostium was occluded for 30 seconds by the inflated balloon without injection, (2) an injection using 1.5 ml. of 30 per cent saline was performed at the same speed as described above while side-holes of the catheter were placed not in the LMC, but in the ascending Ao near the aortic ring, and (3) injection into the LMC was carried out after inducing complete A V block by sectioning distal part of the His bundle during venous inflow occlusion.

Table I Osmolality and pH of fluid utilized for intracoronary injection

	Osmolality (Osm. per Kg. of water)	*pH*
Distilled water	0	7.0
20 per cent hydroxyethyl starch	0.1	6.6
Normal saline	0.3	6.4
20 per cent mannitol	1.1	6.4
76 per cent Urografin	1.4	7.5
10 per cent sodium bicarbonate	1.9	9.5
50 per cent glucose	3.1	3.3
10 per cent saline	3.2	6.3
30 per cent saline	8.5	6.7

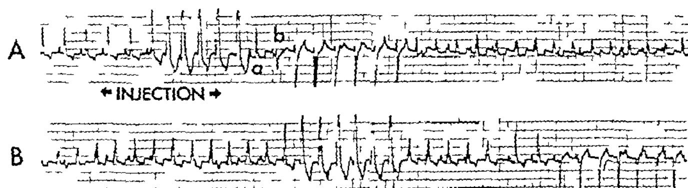


Fig. 5. VT following 30 per cent saline into the LMC under surgical and pharmacologic denervation of the heart. *A*, Sinus rhythm with a rat of 114 per minute before injection followed by slightly irregular VT (rate, about 160). Two fusion beats a and "b were noted. *B* Successive record.

Results

VT without cardiac denervation VT was elicited in all 26 dogs studied by injection into the LMC utilizing the hyperosmotic solutions listed above. Among these hyperosmotic solutions, 50 per cent glucose produced the VT in three of 11 injections (27 per cent) 10 per cent sodium bicarbonate in five of eight (63 per cent) 10 per cent saline in 10 of 16 (63 per cent) and 30 per cent saline in nine of nine (100 per cent) respectively Neither distilled water (four injections) nor normal saline (11 injections) could produce VT and hyposmotic starch also did not (three injections) The VT was not induced by the hyperosmotic solutions having relatively lower) y 20 per cent mannitol (three injec) or 76 per cent Urografin (seven injections). Ventricular rate at its peak during paroxysms of VT was 176 ± 39.2 beats *per minute (mean* ± S.D) ranging from 108 to 300 in all 26 dogs, which was 163 ± 48.4 by 50 per cent glucose, 159 ± 23.6 by 10 per cent sodium bicarbonate, 179 ± 22.5 by 10 per cent saline and 194 ± 58.7 by 30 per cent saline respectively And ventricular rate at the beginning (mean value from initial six beats) was 138 ± 27 6 beats per minute which differed significantly from the maximum rate (176 ± 39.2) ($p < 0.001$)

The latency was defined as the time interval between the beginning of the injection and the appearance of the first beat of the e oked VT Over-all latency was 4 4 ± 5 3 seconds ranging from 0.6 to 17 0 seconds Latency for the VT by 50 per cent glucose was 11 0 ~ 8 seconds 1 ~ 3 1 seconds by 10 per cent sodium bicarbonate 4.3 ± 5 6 seconds by 10 per cent saline and 1 1 ± 0.28 seconds by 30 per cent saline, respectively

Mean duration *of all the VT was 5.8 ± 3.6* minutes *(range, 14 seconds to 18 minutes)*

Commonly the VT started by short runs of ventricular premature beats with rather irregular intervals, where fusion and ventricular capture beats were seen, and A V dissociation was also distinctly observed in this stage (Fig. 2) Thereafter *P* waves became less and less *distinguishable*, culminating in the disappearance of *P* waves, associated with regular R R interval and uniform QRS configuration (Figs. 2 to 6) After the establishment and succession of the VT with regular ventricular rate and QRS complex, abrupt cessation of the VT was rare, which was observed in *two of 27 paroxysms of VT* In most VT A V dissociation (Fig. 2) recurrence of short paroxysms *of VT short runs of, or solitary* ventricular premature beats were observed before the cardiac rhythm was completely restored to the normal sinus rhythm. Transition to ventricular fibrillation (Fig. 4) was noted in two paroxysms of VT (7 per cent) and spontaneous termination of VT was obtained in the remaining 25 VT (93 per cent) Polarity of QRS complex in Lead II of ECG during VT was not definitive at all positive, negative, and biphasic QRS could be seen in the VT produced by a single injection in most experiments (Fig. 2). Arrhythmias of only ventricular origin were found in the present experiment, VT ventricular fibrillation solitary or short runs of ventricular premature beats. It was observed that intracoronary injection of hyperosmotic solutions *into the LMC did not cause* either sinus slowing or supraventricular arrhythmias. Hyperosmotic

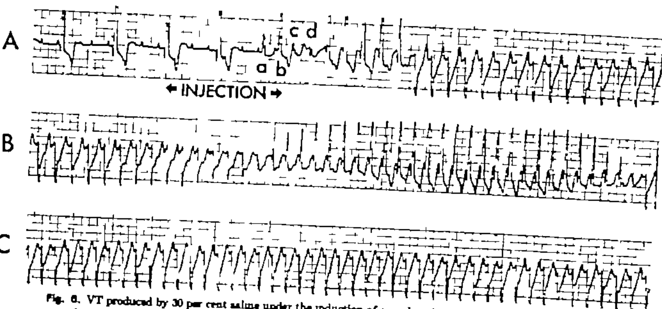


Fig. 6. VT produced by 30 per cent saline under the induction of complet A V block, where atrial rate was 145 per minute and ventricular rate was 46 A, Four ventricular premature beats (" to d"), irregular both in shape and intervals, preceded rather regular paroxysms of VT B, Successiv record. C, Tw minutes after the injection. Ventricular rate reached 1 5 at its peak

lutions evoking the VT also produced solitary ntricular premature beats or short runs as well. jections using distilled water or hyposmotic droxyethyl starch did not cause even an plated ventricular premature beat.

Effects of cardiac denervation Bilateral vagot ny at the cervical level was performed in three gs, and sectioning of the upper part of the oracic vagal trunk was done in one animal. In these four animals VT was elicited by the perosmotic solutions, 10 per cent sodium bicar nate in the one dog (in one of three injections), d 10 per cent saline in the other three dogs (in r of five injections)

Total cardiac sympathetic denervation was ried out in five animals. 10 per cent and/or 30 cent saline provoked VT in these of all dogs eight of nine injections)

lassic total cardiac denervation was made in dog, which did not prevent production of the by 30 per cent saline (in two of two injec s).

ropranolol was administered intravenously at uantity of 0.6 mg. per kilogram in two dogs ch had undergone classic total cardiac dener on. The VT was evoked by 10 and 30 per cent e in these two dogs (in four of four injec s) Furthermore, additionally administered atropine (0.15 mg. per kilogram intravenously) in the other two dogs did not effectively block the induction of VT with 30 per cent saline (in three of three injections) (Fig. 5)

No remarkable difference was noted except for shorter duration between the VT produced without cardiac denervation and that under the combined surgical and pharmacologic denervation.

Supplemental data First, effects of simple ostial occlusion of the LMC with an inflated balloon were estimated in five dogs while under Ao-LAD and Ao-LCX bypass grafting; the ECG s, which were taken before and during occlu sion without any injection, were reviewed. There it was found that no VT resulted from simple ostial occlusion.

Secondly in case that injection was performed not into the LMC but into the ascending Ao in close proximity to the aortic ring using 30 per cent saline, five dogs were observed and it was found that no VT was elicited.

Finally the fact was confirmed in two dogs that injection into the LMC with 30 per cent saline produced the VT in four of four injections, also after the induction of complete A V block (Fig. 6). These two dogs were autopsied, to be ascertained that the distal part of the His bundle had been sectioned.

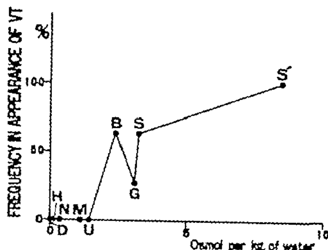


Fig. 7 Relationship between osmolality of injected fluid and frequency in appearance of VT. Frequency represents here the ratio between the number of injections evoking the VT and that of all injections performed for each fluid. D = distilled water. H = 20 per cent hydroxyethyl starch, N = normal saline. M = 20 per cent mannitol, U = 76 per cent Urografin, B = 10 per cent sodium bicarbonate; G = 50 per cent glucose, S = 10 per cent saline, S' = 30 per cent saline.

Discussion

The tachycardia observed in the present experiment appears to be of ventricular origin, because it had the characteristic features of VT the QRS complex with greater duration and with a totally differed pattern from that seen during supraventricular rhythm, A V dissociation fusion and ventricular capture beats (Figs. 2 to 6) At the present time, however it is generally acknowledged that the presence of these phenomena which were considered as specific for the diagnosis of VT are neither definitive nor sufficient criteria for the diagnosis of VT Therefore in the present experiment, the distal part of the His bundle was sectioned to clarify whether the origin of the tachycardia might be supraventricular or ventricular The observation revealed that the tachycardia was produced under the induction of complete A V block (Fig. 6) Hence, it is concluded that the tachycardia is of ventricular origin

The average rate of the tachycardia at its peak during paroxysm was 176 ± 39 2 beats per minutes (ranging from 108 to 300 beats per minute) and 138 ± 27 6 at the beginning (ranging from 96 to 204 beats per minut) respect ely It is known that idioventricular pa makers rarely show a rate of discharge higher than 65 beats per minute even during maximal sympath t timulation and that fast idioventricular rhythm has a rate below 100 beats per minute.[3,4] For these reasons, it does not seem appropriate to define the tachycardia either as idioventricular or fast idioventricular rhythm. Hence, the tachycardia is to be referred as VT It is emphasized that in paroxysms of VT elicited in the present experiment QRS complexes were more widened than during sinus rhythm but were still relatively narrow (Figs. 2 to 6) in comparison with usual (otherwise produced) VT which strongly suggests that ventricular impulses may originate just below the bifurcation of the His bundle.[a]

The VT seems to be neither sympathetically nor vagally mediated, from the finding that it was evoked also under classic total cardiac denervation. This observation is insufficient evidence to conclude that the VT should not be reflexly mediated Intrinsic innervation of the heart also must be taken into consideration. It has been demonstrated that typical ganglion cells and chromaffin like structures [1,] in the myocardium survive after surgical denervation. This intrinsic innervation has seldom been studied functionally [11] and therefore it has not been elucidated whether it has adrenergic or cholinergic activity Anatomical viewpoint favors the concept that the "intrinsic nerves may be parasympathetic post ganglionic fibers and the chromaffin cells. At any rate, it seems that combined classic total cardiac denervation with administration of such massive doses of beta blockade and atropine as in the present experiment can suppress both extrinsic and intrinsic activity of the cardiac nerve. The VT was elicited even under such condition (Fig. 5) This finding strongly suggests that some kind of direct action on the myocardium may be responsible.

Possible explanations for the production of the VT are the following (1) sodium ions, (2) hypoxia, (3) elevated pressure, (4) changes in acidity and (5) hyperosmolality

1 Sodium ions, of course, have a great influence on the heart beat. Indeed, in the series of experiments, solutions of sodium salt (sodium bicarbonate and saline) provoked the VT at the same time, however a sodium free solution (glucose) also produced the VT quite indistinguishable in quality For this reason the VT seems unlikely to result only from highly concentrated sodium ions.

2. Hypoxia results undoubtly from the dilution of blood in the LMC with any injected solutions. Because the chronotropic response to hypoxia is known to be a slower reaction which is commonly measured in minutes rather than in seconds, hypoxia could not be the explanation for the VT having such shorter latency as 4.4 ± 5.3 seconds. Moreover the finding that no VT was induced by distilled water normal saline, or other solutions despite hypoxia in the LMC supports the concept.

3. A slight pressure rise in the LMC was expected from the injection in the present experiment because of imperfect ostial occlusion and the slow rate of injection. If the pressure had increased abruptly sinus slowing due to bareflex arising from the LMC [14] would have to have been observed. But no sinus slowing was noted in the present experiment (Figs. 2 to 6) Moreover some of solutions utilized for injection (possibly to cause an equal degree of elevated pressure) could not evoke the VT From these observations, elevated pressure does not seem to be the genesis of the VT

4. The fact that both acid (glucose and saline) and alkaline solutions (sodium bicarbonate) produced the VT argues that the VT would not be the result of abruptly changed acidity of the blood in the LMC

5. It was observed that solutions with higher osmolality produced the VT while those with lower osmolality could not.

For these reasons, it is concluded that hyperosmolality is the mechanism of the VT This concept may be favored by the relationships (as shown in Figs. 7 to 9) between osmolality and the following (1) frequency in appearance of VT (number of injections producing VT per all injections of each fluid) (2) maximum ventricular rate during paroxysm of VT and (3) latency

It seems quite unlikely that any direct effect on the myocardium would result from transfer of injected solutions through the thick wall of the LMC, and so it appears more reasonable to consider that these solutions, which were carried by way of the branches of the LMC caused some changes in the myocardium to elicit the VT Eckstein and associates[15] have demonstrated that there are some branches arising from the LMC in dogs, in contrast to the traditional concept that the LMC would be a mere conduit for the blood

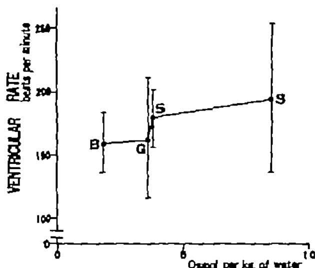


Fig 8. Relationship between osmolality and ventricular rate at its peak during paroxysm of VT Vertical lines represent S.D.

to pass to the LAD and LCX. It has been accepted that abruptly elevated pressure in the LMC causes sinus slowing resulting from vagally mediated baroreflex. [14] In this laboratory also, it has been confirmed in another experiment that sinus slowing can be induced by arterial blood or normal saline injected at a rapid rate into the LMC under perfect ostial occlusion. For this reason, it is necessary to avoid a sudden increment of pressure in this artery left coronary ostial occlusion must be incomplete to avoid activating the baroreflex as in the present experiment, permitting leakage of some quantities of injected solutions from the LMC to the ascending Ao. The supplemental data described above show that no injection into the ascending Ao utilizing hyperosmotic solutions caused the VT which indicates that the injected solutions, in spite of leakage, have an effect on the myocardium to elicit the VT by way of branches arising from the LMC to heart muscle, not by transfer of the solutions to the Ao or its branches, including carotid and right coronary arteries.

Summary

Ao-LAD and Ao-LCX bypass graftings were made in 28 mongrel dogs anesthetized with pentobarbital sodium. Selective injection into the LMC was carried out at a speed of 0.5 ml. per second using a 1.5 ml. quantity of the following fluid. distilled water 20 per cent hydroxyethyl starch

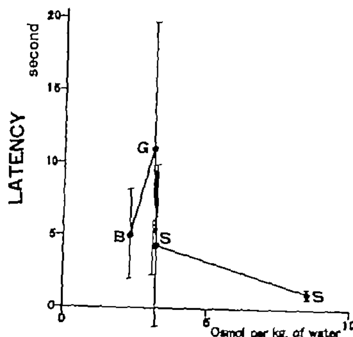


Fig. 9 Relationship between osmolality and latency of the evoked VT

(pH 6.5 0.1 Osm per kilogram of water) normal saline (pH 6.4 0.3 Osm. per kilogram of water) 20 per cent mannitol (pH 6.4, 1.1 Osm. per kilogram of water) 76 per cent Urografin (pH 7.5 1.4 Osm per kilogram of water) 10 per cent sodium bicarbonate (pH 9.5 1.9 Osm. per kilogram of water) 50 per cent glucose (pH 3.3, 3.1 Osm per kilogram of water) 10 per cent saline (pH 6.3 3.2 Osm. per [illegible] of water) and 30 per cent saline (pH 6.7 [illegible] Osm. per kilogram of water).

Injection of 50 per cent glucose produced VT in 27 per cent of the animals, 10 per cent sodium bicarbonate produced VT in 63 per cent, 10 per cent saline did the same in 63 per cent, and 30 per cent saline produced VT in 100 per cent, respectively. Other fluids did not evoke VT. The ventricular rate of VT at its peak was 176 ± 39.2 beats per minute, and the QRS complexes during paroxysms were, of course, wider than during sinus rhythm but rather narrower than usual (otherwise produced) VT.

The VT was elicited under classic total cardiac denervation and under additionally administered propranolol (0.6 mg. per kilogram intravenously) with atropine (0.1 mg. per kilogram). Also, the induction of A V block by sectioning the distal part of the His bundle did not effectively block the production of VT.

The data obtained from the present experiment suggest the following. (1) Hyperosmolality is the mechanism of the VT. (2) This VT is not reflexly mediated either extrinsically or intrinsically but it may result from a direct action on the myocardium. (3) Ventricular impulses may originate from just below the bifurcation of the His bundle. (4) The LMC may supply blood to the myocardium by way of its own branches.

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Electrophysiological and antiarrhythmic effects of lidocaine in canine acute myocardial ischemia

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Extrapolation of electrophysiologic properties of antiarrhythmic drugs determined by *in vitro* studies on isolated cardiac tissue to the *in situ* heart has many problems. In myocardial ischemia these problems may be particularly important since differences in action potential duration, refractoriness, and conduction between ischemic and normal zones may be important in the genesis of arrhythmias and their abolition by antiarrhythmic agents. Propranolol for one has been found to diminish the difference in monophasic action potential duration between ischemic and normal zones and this effect may be important in its antiarrhythmic properties.

In a previous study we determined the effects of a constant rate infusion of lidocaine on conduction and refractoriness in infarcted and normal zones 2 to 6 hours following coronary artery ... We found that lidocaine prolongs conduction and refractoriness in the infarcted but not in the normal zone. These properties of lidocaine may be important in its antiarrhythmic effects, though slowing of intraventricular conduction could provoke ventricular arrhythmias as well as curtail them. In the present study the electrophysiologic effects of lidocaine were determined in a model of canine acute myocardial ischemia in which effects on ventricular arrhythmias were correlated directly with effects on electrophysiologic parameters.

The technique of paired 15 minute coronary artery ligations which are associated with reversible structural, histochemical, and electrophysiologic (i.e., ST segment) changes was used to examine the effects of lidocaine on monophasic action potential duration (APD), effective refractory period (ERP), and the occurrence of ventricular arrhythmias during acute ischemia.

Methods

In adult mongrel dogs anesthetized with pentobarbital (30 mg./Kg. intravenously) and mechanically ventilated, a midsternal thoracotomy was performed and the heart exposed. Silver electrodes embedded in acrylic plaques were sewn onto the right atrium, the lateral right ventricular epicardium, and the left ventricular epicardium in the distribution of the left anterior descending coronary artery. A suction electrode, which consisted of silver wire placed within polyethylene tubing, was also placed on the lateral right ventricular epicardium. A ligature in the form of a sling was placed around the left anterior descending coronary artery distal to the first or second diagonal branch so that repeated ligations and releases of the artery could be performed.

The protocol for the study was as follows. Control ligations of the left anterior descending coronary artery were performed for 15 minutes. Bipolar atrial pacing was performed at constant R-R intervals in each dog (300 to 350 msec. between dogs), and continuous ECG recordings were made. Bipolar electrograms were recorded

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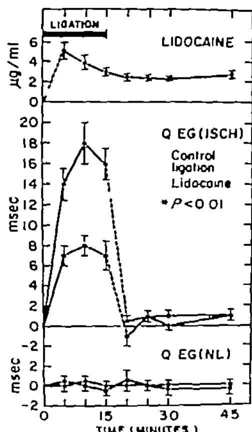


Fig. 1 Effect of lidocaine on conduction intervals in the ischemic zones. Open circles (o) show mean determinations made during control ligations and closed circles ( ) show those made during ligations in which lidocaine was administered. *Top panel* shows blood lidocaine levels ± SE. *middle (Q-EG (ISCH))* and *bottom (Q-EG (NL)) panels* show changes in Q-EG intervals in the ischemic and normal zones, respectively. Each point on the curves of the bottom two panels represents the mean differences in msec. ± SE between values obtained after coronary artery ligation and those obtained just prior to ligation. The asterisks ( ) indicate p < .01 between control Q-EG intervals paired with those obtained with lidocaine. See text for further discussion.

from the normal zone on the right ventricle and from two pairs of electrodes in the ischemic zone between filter frequencies of 12 to 500 Hz for the 15 minutes of the ligation and for 30 minutes after the ligature was released. Monophasic action potentials were recorded from ventricular muscle in the ischemic and normal zones at 15 minutes of coronary artery ligation between filter frequencies of 0.1 to 500 Hz. For these recordings, bipolar epicardial electrodes were utilized in the normal zone one of the electrode pair was a suction electrode.

One hour after the above recordings had been made, a second coronary artery ligation was performed and immediately after ligation commercially available lidocaine for cardiac use (Xylocaine Astra) was administered as a 2 mg./Kg. intravenous bolus followed by a constant rate intravenous infusion of 70 μg/Kg./minute for 45 minutes. The same recordings at the same time after ligation were made as in the control ligation and in addition, blood lidocaine levels were determined. In four dogs, lidocaine was administered with the first ligation and control ligations were performed 2 hours after termination of the lidocaine infusion. Blood lidocaine levels at the time of the second ligation in these dogs were 0.5 μg/ml. or less and the results were similar to and not significantly different from those obtained for dogs in which control ligations were performed first. The data from all dogs were grouped.

During each ligation the number of ventricular beats occurring per minute in all but the first 2 minutes was determined. Monophasic action potential duration was determined from recordings made by the suction electrodes in the normal zone and the epicardial electrode in the ischemic zone. Monophasic action potential duration determined by the use of suction electrodes has been found to reliably reflect the duration of an action potential that would be recorded from the same site with an intracellular electrode.[14] Also with the use of a specially fashioned tripolar electrode in which one pole was a suction electrode and the other two were surface electrodes, we have determined that epicardial electrodes in ischemic tissue record monophasic potentials of the same duration as do suction electrodes at the same site.

Effective refractory period (ERP) was determined at 15 minutes of ligation by means of programmed premature stimuli of 2 times diastolic threshold delivered after every tenth atrial paced beat. Intervals (Q-EG) were measured from the initial deflection in the QRS complex of the limb lead ECG to the major deflection of the bipolar electrograms in the ischemic and normal zones.

If ventricular fibrillation occurred during the control ligation or the ligation in which lidocaine was administered, the study could not be completed and these dogs were not included in the results. When ventricular fibrillation occurred following ligature release and successful electroconversion was performed with a single electric shock of 50 joules or less, the dogs were

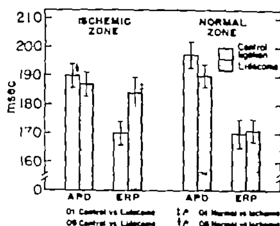


Fig 2. *Effect of lidocaine on mean monophasic action duration (APD) and effective refractory period (ERP) in the ischemic and normal zones.* Values were determined 15 minutes after coronary artery ligation. *The vertical bars* show mean values in msec. ±SE during control ligations (*clear bars*) and those in which lidocaine was administered (*stippled bars*). $(p < .01)$ and $\dagger(p < .05)$ indicate statistical significance when control values were paired with those obtained with lidocaine. $\ddagger(p < .01)$ and $\S(p < .05)$ indicate statistical significance when values obtained in the ischemic zone were paired with corresponding values obtained in the normal zone. See text for further discussion.

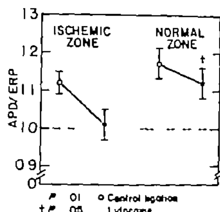


Fig 3. Effect of lidocaine on APD/ERP. Values are mean ±SE. See text for further discussion. $* = p < .01$, $\dagger = p < .05$.

included in the study. Coronary artery ligations were performed in 24 dogs. Of these 16 form the basis of the present study; the remaining eight dogs were not included because of the occurrence of ventricular fibrillation during ligation.

Blood lidocaine concentrations were determined by gas chromatography and were performed by the Astra Corporation. Evaluation of statistical significance was performed using the paired Student's t test in which control determinations were paired with values obtained in the same dogs during the ligations in which lidocaine was administered.

Results

Within a few minutes after the control artery ligation, there was discoloration of cardiac tissue in the zone supplied by the ligated artery and the occurrence of a monophasic potential. Within 5 minutes there was significant delay of activation in the ischemic zone (Fig 1). In addition ventricular beats occurred, the frequency of which generally reached their peak between [illegible] to 10 minutes and then declined.

During coronary artery ligations mean blood lidocaine levels ranged from [illegible] µg/ml (5 minutes) to 3.0 µg/ml [illegible] minutes) (Fig. 1 *upper panel*). In the 30 minutes following release of the ligature, mean blood lidocaine levels ranged from 2.5 to 2.8 µg/ml. These blood lidocaine levels are within the range that has been considered therapeutic, and in this study lidocaine reduced the frequency of ventricular beats from a mean of 17 per minute during control ligations to a mean of 8 per minute $(p < .01)$. While lidocaine was having these antiarrhythmic effects during ligation, it caused changes in APD, ERP, the APD/ERP ratios (Figs. 2 and 3) and conduction intervals (Figs. 1 and 4).

The effects of lidocaine on mean APD and ERP in the ischemic and normal zones are shown in Fig. 2. In the ischemic zone, lidocaine did not significantly change APD but it prolonged ERP from 170 ± 4 to 184 ± 5.5 msec. $(p < .01)$. In the normal zone, lidocaine reduced APD from 198 ± 5 to 190 ± 3.5 msec. $(p < .05)$ but had no significant effect on ERP. It is also of note that during the control ligation mean APD in the ischemic zone (190 msec.) was 8 msec. less than in the normal zone (198 msec. $p < .05$) while with lidocaine the difference in APD between ischemic and normal zones declined to 3 msec. and was not significant. Further, during the control ligation mean ERP's in the ischemic and normal zones were not significantly different (1 msec.) while with lidocaine, ERP in the ischemic zone became significantly greater than in the normal zone (13 msec. $p < .01$). This contrasts with the results 2 hours following coronary artery ligation when ERP in the infarcted zone was shorter than in the normal zone and lidocaine reduced the difference.

Fig. 4 shows the effect of lidocaine on the ratio

of APD to ERP in the ischemic and normal zones. Lidocaine reduced APD/ERP in the ischemic zone from 1.12 ± 0.03 to 1.02 ± 0.04 ($p < .01$) and in the normal zone to a lesser extent from 1.17 ± 0.05 to 1.12 ± 0.05 ($p < .05$).

The effects of lidocaine on conduction intervals in the ischemic and normal zones were similar to those found in a previous study 2 hours after coronary artery ligation. Fig. 4 shows an example of these effects and Fig. 1 shows the data for Q-EG intervals in the ischemic and normal zones as well as serum lidocaine levels.

During the control ligations there was a mean prolongation of 7 to 8 msec. in conduction intervals in the ischemic zone which returned to preligation values within 5 minutes after release of the ligature (Fig. 1). With lidocaine there was a greater mean prolongation of Q-EG in the ischemic zone of 14 to 18 msec. with peak difference of 10 msec. between lidocaine and control at 10 minutes. Following release of the ligature, Q-EG intervals in the ischemic zone rapidly declined and within 5 minutes were not significantly different from those after release of the control ligation in spite of the fact that blood lidocaine levels of 2.5 to 2.8 μg/ml. were maintained by the constant rate infusion (Fig. 1). In the normal zone, Q-EG intervals were not significantly changed either during the control ligation or with lidocaine. QRS duration was also determined and was also not significantly changed by lidocaine, as has been previously reported.

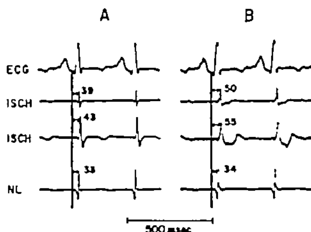


Fig. 4. Example of the effect of lidocaine on Q-EG intervals recorded in the ischemic and normal zones. *The top trace (ECG)* shows ECG Lead II, *the 2nd* and *3rd traces (ISCH)* show bipolar electrograms recorded in the normal zone 15 minutes after left anterior descending coronary artery ligation. ECG were recorded at 0.1 to 500 Hz and electrograms were recorded at 12 to 500 Hz. *The vertical line* shows the onset of the QRS complex. During the control ligation *(A)* the intervals from the onset of the QRS complex to the major deflection of the local electrograms (Q-EG) were 39 and 43 msec. in the ischemic zone and 33 msec. in the normal zone. During the ligation in which lidocaine was administered *(B)*, Q-EG intervals were prolonged to 50 and 55 msec. in the ischemic zone but remained virtually the same (34 msec.) in the normal zone.

Discussion

In the present study the electrophysiologic effects of lidocaine in acute myocardial ischemia were determined and correlated with its effects in curtailing ventricular arrhythmias. Lidocaine shortened APD only in the normal zone and prolonged ERP only in the ischemic zone. Lidocaine also prolonged conduction only in the ischemic zone.

Several differences in conditions present in ischemic and normal zones may cause lidocaine to have different properties in these zones. For example, lidocaine may shorten APD only in the normal zone for the following reasons. During control ligations in the present study (Fig. 2) as well as in other studies,[14] APD was shorter in the ischemic than in the normal zone perhaps, in part, because of increased potassium conductance during repolarization due to elevated local potassium concentration. In normal ventricular muscle *in vitro* lidocaine shortens APD, an effect also thought to be due to increased potassium conductance[19] and this effect may be blunted in the ischemic zone where potassium conductance is already higher.

The selective depression of conduction in the ischemic zone can be explained by the sensitivity of partially depolarized cells to the local anesthetic effects of lidocaine.[20, 22] In partially depolarized Purkinje fibers and ventricular muscle of guinea pigs, sheep, and dogs, lidocaine markedly depresses the Vmax of phase 0 of the action potential, a parameter which correlates with the rate of conduction of impulses, while in cells with normal resting potential lidocaine has little or no effect on Vmax.[20-22] This action of lidocaine contrasts with another local anesthetic agent quinidine, which depresses Vmax proportionately at all levels of resting potential.[20] Since cells in the ischemic zone are partially depolarized due to locally elevated potassium levels,[13] acidosis, cellular injury or other factors, they would be much more sensitive to the depressant effects of

lidocaine than would cells in the normal zone

The effects of lidocaine on ERP observed in the present study may be related to recovery kinetics. Recovery of channels for rapid inward current is voltage dependent in normal Purkinje fibers and ventricular muscle and thus occurs during phase 3 of the action potential, though in depressed Purkinje fibers and ventricular muscle, recovery may be time rather than voltage dependent. Lidocaine delayed recovery of channels for rapid inward current,[16, 22] delayed the time during and after the action potential when a stimulus can initiate a new action potential, and therefore prolonged the refractory period relative to action potential duration (i.e., diminishes the APD/ERP ratio). Since lidocaine shortens APD in normal Purkinje fibers and ventricular muscle, it may slightly shorten, have no effect on, or prolong absolute ERP in these tissues by virtue of its effect in prolonging ERP relative to APD (diminishing APD/ERP). In the present study lidocaine diminished APD/ERP in the normal zone (Fig. 3) consistent with *in vitro* studies while over-all it shortened APD and caused no change in absolute ERP. Lidocaine also diminished APD/ERP in the ischemic zone but did not change APD and consequently it prolonged absolute ERP. Also of possible importance is the fact that delay of recovery of channels for rapid inward current induced by lidocaine *in vitro* was more marked in partially depolarized ventricular cells,[16] which may explain why there was a greater reduction of APD/ERP in the ischemic than in the normal zone (Fig. 3).

Other factors which may explain lidocaine's different effects in the ischemic and normal zones such as the possible role of metabolites, have been discussed previously. It is also worth noting that selective inhibition of slow inward current would not explain lidocaine's effects in the ischemic zone, since the drug does not inhibit this current.

From the data on the interplay of APD and ERP between ischemic and normal zones in the present study and the data on conduction intervals in the ischemic zone in both the present and previous studies one can make certain speculations on the electrophysiologic properties responsible for lidocaine action against ventricular arrhythmias in the *in situ* heart. First, it should be noted that ventricular arrhythmias occurring early after coronary artery ligation are probably reentrant rather than automatic since ventricular automaticity is not increased at this time.[24, 25] Important causes of reentry are slowing of conduction, which as shown here (Fig. 1) and by others[3, 26] occurs in ischemic zones, and unidirectional block. Lidocaine may abolish these reentrant cycles by further slowing conduction to the point of block or by prolonging refractoriness in the ischemic zone, thus causing two-way block where there was previously one-way block.[19]

Another possible cause of reentry is boundary current which arises in acute ischemia because of differences in APD between ischemic and normal zones. The shorter APD in ischemic zones (Fig. 3) causes the creation of potential differences with flow of depolarizing current and, therefore, propagation of re-entrant impulses from the normal to the ischemic zone. The relatively slow conduction in the ischemic zone enhances this mechanism.

In the present study two actions of lidocaine could have suppressed reentry due to boundary currents. First, lidocaine significantly shortened APD only in the normal zone (Fig. 2). This effect caused APD in the ischemic and normal zones to be more nearly equal, and thus diminished the differences in potential in the latter part of the action potential. Secondly lidocaine lengthened refractoriness in the ischemic zone (Fig. 2) and decreased the APD/ERP ratio. Because of these effects, reentrant impulses due to boundary currents would encounter more refractory tissue as they are transmitted back from normal to ischemic zone during the latter part of the action potential and thus would be less likely to propagate further.

It is also of interest that by selectively prolonging ERP in the ischemic zone, lidocaine increased the disparity in ERP between zones (Fig. 2). It has been thought that an increased disparity of ERP between different zones of the heart results in arrhythmias,[27] in part because it reflects a disparity in APD which is the cause of the boundary currents. However in the present study lidocaine reduced the disparity in APD while it increased that of ERP. These findings show that changes in disparity of ERP do not necessarily reflect similar underlying changes in APD and that an increased disparity in ERP of itself is not necessarily associated with arrhythmogenicity. In fact, as noted above, the selective prolongation of ERP induced by lidocaine in the ischemic zone

probably tended to curtail rather than promote arrhythmias.

From the above data it is apparent that in considering lidocaine's antiarrhythmic properties, one must carefully consider its effects on the interplay that occurs between normal and abnormal cardiac tissue in the diseased heart, and not only its effects on individual cardiac cells. Propranolol also has certain electrophysiologic effects in myocardial ischemia which would curtail arrhythmias. Like lidocaine, it prolonged conduction only in the ischemic zone, prolonged ERP in the ischemic zone, and diminished the disparity in APD between ischemic and normal zones at a time when it was diminishing the frequency of ventricular beats.

Finally one aspect of the present study should be taken into account when administering lidocaine to patients with ischemic heart disease and conduction abnormalities. It has been thought that lidocaine is a relatively safe drug to administer to these patients since it would not cause progression of conduction abnormalities or complete heart block. However because lidocaine slows conduction in ischemic tissue, it certainly could cause conduction abnormalities to occur or cause existing abnormalities to progress. There is further evidence of this in the reported progression of conduction abnormalities in certain patients when lidocaine was administered.

Summary

The electrophysiologic effects of temporary (15 minute) ligations of the left anterior descending coronary artery were examined in 16 dogs. Monophasic action potential duration (APD) and effective refractory period (ERP) were determined in the ischemic and normal zones. Intervals (Q-EG) were measured from the onset of the QRS in a standard ECG lead to the major deflection of electrograms recorded in these zones. Control ligations were compared to those in which a 2 mg/Kg. intravenous bolus of lidocaine was administered immediately after ligation followed by a constant rate intravenous infusion of 70 µg/Kg/minute. Lidocaine reduced the number of ventricular beats per minute (17 to 8) ($p < .01$) and at the same time it prolonged ERP only in the ischemic zone (14 msec., $p < .01$), shortened APD only in the normal zone (8 msec., $p < .05$), reduced APD/ERP in the ischemic zone (1.12 to 1.01 $p < .01$) and to a lesser extent in the normal zone (1.17 to 1.12; $p < .05$) and it prolonged conduction only in the ischemic zone (10 msec. at peak effect, $p < .01$). During the control ligation APD in the ischemic zone was 8 msec. shorter than in the normal zone ($p < .05$) while with lidocaine the difference was reduced to 3 msec. (N.S.) The effects of lidocaine reducing the disparity in APD between ischemic and normal zones in prolonging conduction and refractoriness in the ischemic zone and in reducing APD/ERP may explain the demonstrated antiarrhythmic properties in acute myocardial ischemia.

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Case reports

Spontaneous dehiscence of an aortic commissure complicating idiopathic aortic root dilatation

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Rupture of the aortic valve is a well recognized, but uncommon, phenomenon, first described in 1830. Aortic valve rupture secondary to trauma or exertion has been described. Non traumatic aortic valve rupture has been noted in bacterial endocarditis, syphilis, fenestrated aortic valves, valves with myxomatous transformation,[12] cystic medionecrosis of the aorta, and in inherited disorders of connective tissue. We present two cases of spontaneous dehiscence of the aortic valve commissure in the presence of isolated aortic root dilatation, with no evidence of a connective tissue disorder and unrelated to trauma or exertion.

Observations

Case No. 1. A 47-year-old black male was in good health until 2 days prior to admission when he noted the onset of shortness of breath. He denied any chest discomfort. His past medical history was unremarkable, with no history of heart disease or hypertension. On admission he was in pulmonary edema, with a blood pressure of 170/50 mm. Hg, a III/VI early diastolic murmur of aortic insufficiency, a III/VI systolic ejection murmur along the left sternal border, and peripheral signs of aortic insufficiency. There were no peripheral manifestations of endocarditis. The chest x-ray showed minimal cardiomegaly and bilateral perihilar alveolar infiltrates. The electrocardiogram showed left ventricular hypertrophy. Aortography demonstrated dilatation of the aortic valve ring and proximal ascending aorta with severe aortic regurgitation (Fig. 1). There was no evidence of dissection. He was diuresed and stabilized hemodynamically, but deteriorated neurologically and became comatose. He had cardiac arrest on the fifteenth hospital day and died suddenly. The STS and all blood cultures were negative.

At autopsy the heart was enlarged, weighing 660 grams. The right ventricle and atrium were dilated and the left ventricle was hypertrophied. The ascending aorta and aortic ring were dilated with minimal fragmentation of medial elastic fibers. There was no evidence of aortic dissection or aortitis and aortic atherosclerosis was minimal to moderate. The commissure of the left coronary and non-coronary cusps of the aortic valve was avulsed from its base on the aorta (Fig. 2). The aortic valve leaflets were otherwise unremarkable.

Case No. 2. A 73-year-old white female was in good health until the morning of admission when she woke with severe shortness of breath. She denied any chest discomfort. The past medical history was unremarkable with no history of cardiac disease or hypertension, but she had not seen a physician in over 10 years. On admission to another hospital she was in pulmonary edema with prominent jugular venous distention, a blood pressure of 120/80 mm. Hg, a II/VI systolic ejection murmur and a III/VI early diastolic murmur of aortic insufficiency both heard along the left sternal border, and peripheral signs of aortic insufficiency. There were no peripheral manifestations of endocarditis. Chest x-ray demonstrated moderate cardiac enlargement with bilateral pleural effusions, fluid in the fissures, and prominent vascular markings. Electrocardiogram showed poor R wave progression across the precordium and frequent PVC's. Blood cultures were negative. She had a positive STS and a positive FTA. After an initial diuresis she was stable hemodynamically until 20 days after admission when she noted acute onset of shortness of breath, with recurrence of pulmonary edema and a louder diastolic murmur. She was transferred to The Johns Hopkins Hospital where cardiac catheterization demonstrated marked dilatation of the aortic sinuses and proximal ascending aorta with moderate aortic regurgitation. There was uncoiling and tortuosity of the thoracic aorta but no evidence of dissection (Fig. 1). She was scheduled for aortic valve replacement but had cardiac arrest and died during induction of anesthesia, 30 days after onset of symptoms.

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Fig. 1. A and B. *A*, Aortogram in Case 1 showing moderate aortic root dilatation and regurgitation of contrast medium into the left ventricle. *B*, The aortogram in Case 2 shows marked aortic root dilatation and tortuosity and kinking of the distal aorta. Contrast material regurgitates into the left ventricle.



Fig. 2. A and B. Case 1. *A*, View of aortic valve from downstream aspect. The commissure of the left coronary and non-coronary cusps has separated from the aortic wall *(arrow)*. *B*, Opened aortic valve with dehiscent commissure *at the arrow*. The commissure of the right coronary-noncoronary cusps shows trivial fusion.

At autopsy the heart [illegible] preceding case had be[illegible] studied [illegible] raph and formalin [illegible] ascending aorta [illegible] near the aortic [illegible] aorta. There was [illegible] media, but no eviden[illegible] dilated and hypertrophied [illegible] ened with rolling of the edg[illegible] of the commissure of the [illegible] commissure of the righ[illegible] cusps was avulsed from the ao[illegible]

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Discussion

Sudden onset of severe congestive heart failure in the presence of a new or markedly increased murmur of aortic insufficiency is characteristic of rupture of the aortic valve. As noted previously both traumatic and non traumatic aortic [illegible] rupture have been described. We have reported two cases of spontaneous dehiscence of an aortic [illegible] commissure in the presence of idiopathic dilatation of the ascending aorta. There was no

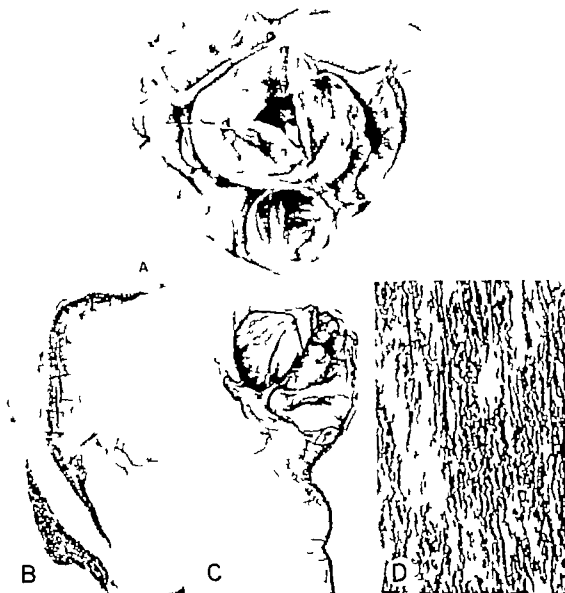


Fig. 3, A through D. Case 2. *A*, Base of the heart viewed from atrial aspect. The aortic root and valve ring are markedly dilated. The pulmonary trunk and valve ring (normally slightly larger than the aorta) are of normal diameter. The commissure of the right coronary and noncoronary cusps *(arrow)* is separated from its attachment to the aortic root. *B*, Section taken at level of arrow in *A* to show the avulsed commissure. (Verhoeff-van Gieson elastic stain, original magnification ×3). *C*, Edge of the mid-portion of the valve cusp showing the nodule of "rolling." The degree of development of the rolling indicates that some degree of aortic regurgitation had probably been present for years (Verhoeff-van Gieson elastic stain, original magnification ×15). *D*, Aortic media in the dilated ascending aorta showing fraying and fragmentation of the elastic lamellae. The aortic wall was thin in the dilated part but showed no evidence of inflammation or healed syphilitic mesaortitis. (Verhoeff-van Gieson stain, original magnification ×150).

evidence of connective tissue disorder in either case. We believe the dilatation of the aorta was the primary event, with secondary fragmentation of the elastic media, as has been noted in post stenotic aortic dilatation.[17] In Case No. 2, the ascending aorta was more widely dilated, and the elastic media more fragmented than in Case No 1. The thickened and rolled cusps, fused commissures, and left ventricular dilatation in Case No 2 suggest that the aortic root dilatation and secondary minimal aortic insufficiency was of several years duration. A murmur of aortic insufficiency had not been noted previously in Case No 2, but she was asymptomatic and had not

seen a physician for over 10 years prior to the present illness. Case No 1 had no history of heart disease and no evidence of aortic valve disease or left ventricular dilatation at autopsy The sudden onset of severe congestive heart failure was due to spontaneous dehiscence of the aortic valve commissure in both cases.

Spontaneous rupture of an aortic valve cusp in the presence of cystic medionecrosis of the aorta both with and without evidence of a connective tissue disorder has been described.[3-16] We have reported two cases of spontaneous dehiscence of an aortic valve commissure in the presence of dilatation of the ascending aorta and secondary fragmentation of the elastic media with no evidence of a systemic connective tissue disorder Prompt recognition of the condition and surgical intervention with aortic valve replacement is probably the only effective treatment of aortic valve rupture.

Summary

Two patients had spontaneous dehiscence of an *aortic commissure producing severe aortic regur* gitation. There was dilatation of the aortic root in both cases which could not be attributed to inflammation, syphilis, or a connective tissue disease. Valve ring dilatation probably renders the valve susceptible to rupture by altering the relationship of the cusps to each other thus weakening their mutual support during diastole.

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The use of the diving reflex to terminate supraventricular tachycardia in a 2 week-old infant

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Paroxysmal supraventricular tachycardia (PST) is a treatable cardiac emergency. Unfortunately reflex vagal stimulation by carotid sinus and unilateral eyeball pressure, induction of vomiting, breath holding, or the Valsalva maneuver are rarely successful in terminating the tachycardia in children, particularly small infants. Other standard forms of therapy such as rapid intravenous digitalization and direct current counter shock carry some significant risks. Stimulation of the diving reflex by immersion of the face in cold water has been noted to terminate attacks of supraventricular tachycardia in adults[1-3] and children. There is one recent report of the use of the diving reflex to terminate PST in two infants. We wish to report successful use of the diving reflex to terminate an attack of PST in a 14-day-old infant and to emphasize the need for careful control of the temperature of the water bath used for facial immersion.

Case report

Patient J. D. was a 14-day-old female, the product of full-term spontaneous vaginal delivery to a 33-year-old gravida 3 para 3 female who had no problems during pregnancy labor or delivery. The birth weight was 6 pounds, 11½ ounces. The infant had been intermittently tachypneic from birth, but had fed well until 12 days of age when she became severely tachypneic and began vomiting. The next day she was brought to the University of Wisconsin Childrens Hospital where her admission electrocardiogram showed supraventricular tachycardia with a rate of 300 (Fig. 1). She was noted to be in acute congestive heart failure with poor tissue perfusion.

Carotid massage and unilateral eyeball pressure were not successful in terminating the tachycardia. Intravenous digitalization ([illegible] mg./M.²) was instituted with half the calculated total digitalizing dose given initially. Two minutes later the infant's face was placed in a basin of ice water at 5° C. for 5 seconds. Her nostrils were manually occluded to prevent aspiration. The PST converted to a sinus rhythm of 120 within 3 seconds and within 5 seconds the rate was 150 (Fig. 2). She remained at this rate for 1½ hours at which time PST recurred. Therapy using the ice water bath at 5° C. was reinstituted. Sinus rhythm was restored immediately after facial immersion, but after 10 minutes, PST again developed. This lasted for 5 minutes, at which time she again converted to sinus rhythm without any further intervention. She was digitalized intravenously over 24 hours and remained in sinus rhythm over the next 6 days with resolution of the congestive heart failure. At follow-up examination 2 months following discharge, the infant remains in sinus rhythm with a rate of 140 per minute. There is no evidence on physical examination, chest x-ray or echocardiogram of underlying congenital heart disease. An ectopic atrial pacemaker is noted on the electrocardiogram (Fig. 3).

Discussion

The rapid response of the three reported newborn infants with supraventricular tachycardia to the diving reflex makes this ideal therapy for distressed infants with this arrhythmia. The diving reflex has been discussed by several authors.[4-10] It is generally agreed that it is a vagally mediated response initiated by facial skin sensors and breathholding.[4,10] The diving reflex causes peripheral vasoconstriction and a vagally mediated decrease in cardiac output and heart rate with stable or slightly increased blood pressure. This reflex, then, decreases blood supply to

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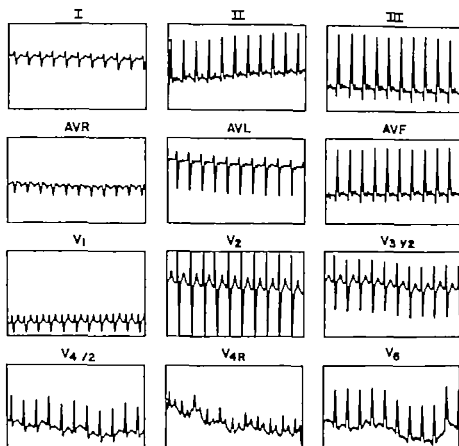


Fig. 1 Twelve-lead electrocardiographic tracing t time of admission demonstrating supraventricular tachycardia with a rate of 300. There are large posterior and inferior forces noted as well as increased anterior forces.

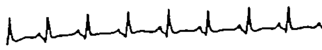


Fig. 2. Rhythm strip 5 seconds following facial immersion demonstrating sinus rhythm with heart rat of 150.

viscera and muscles, but maintains effective blood supply to the brain and heart enabling animals to remain submerged for long periods of time. In man the diving reflex has been demonstrated at birth.

The temperature of the bath used for immersion has been noted to be of importance. The vagal response becomes more profound when the temperature of the bath is reduced below 20° C Hunt and associates, however felt that a temperature of to 4 C was too low and obtained maximal results with a temperature of 18 C. There have been reports of adults who developed ventricular tachycardia when the temperature in an ice bath was below 4 C. after facial immersion for a period of 30 seconds. Perhaps the cold temperature and prolonged immersion resulted in a considerable catechol amine discharge which was responsible for ventricular dysrhythmias. In the three infants reported, the total time of each facial immersion was less than 6 seconds. In the previously reported cases of the use of the diving reflex in children, no mention is made of the temperature of the water bath. The temperature of our bath was 5 C. and we noted no ventricular arrhythmias at that temperature.

We have demonstrated the effectiveness of the diving reflex in treating PST in a 2 week-old infant. The use of the diving reflex is a valuable tool which can be used to convert PST in newborns, especially those with circulatory insufficiency Careful attention must be paid to the temperature of the water bath to avoid causing ventricular dysrhythmias. Since the effect is

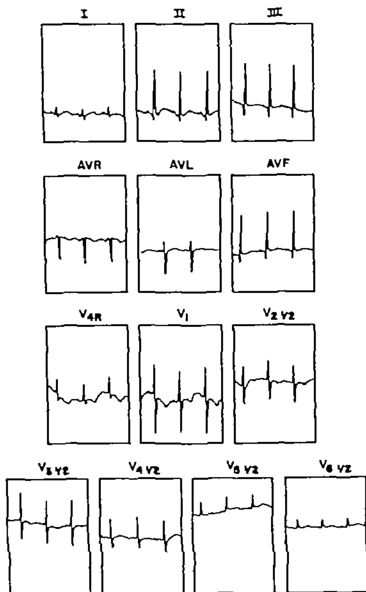


Fig. 3. Twelve-lead electrocardiogram tracing 2 months following discharge demonstrating sinus rhythm with heart rate of 140. An ectopic atrial pacemaker is noted.

short lived, it is important to prevent recurrence of the tachyarrhythmia with an appropriate agent such as digitalis.

Summary

The use of the diving reflex to terminate a case of paroxysmal supraventricular tachycardia (PST) is described in a 2 week-old infant who presented in severe congestive heart failure with supraventricular tachycardia at a rate of 300. The infant's face was placed in a basin of ice water at 5° C for 5 seconds with manual occlusion of the infant's nostrils to prevent aspiration. The PST converted to a sinus rhythm of 120 within 3 seconds of facial immersion. The physiology of the diving reflex is reviewed and the uses and hazards of this reflex in terminating attacks of PST in infants is discussed.

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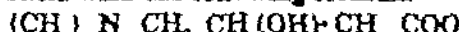
Review

Role of carnitine in fatty acid metabolism of normal and ischemic myocardium

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An increasing emphasis on the role of free fatty acid as fuel for the normal heart[1-4] has culminated in a thorough understanding of the intracellular pathways concerned in the production of energy from fats. At the same time "toxic" cardiac effects of high levels of free fatty acids, as found in acute myocardial infarction, have been described,[5-8] and the possibility of exaggeration of ischemia by fatty acids has been raised.[9] Intracellular accumulation of an intermediate of fatty acid metabolism, acyl CoA, has been found in association with impaired mitochondrial metabolism.[11] These observations have focused attention on the clinical importance of a better understanding of fatty acid metabolism. The purpose of this review is to analyze the physiological and possible therapeutic role of carnitine, a vitamin essential for normal fatty acid oxidation.

Carnitine is a water-soluble naturally occurring aminoacid with the following formula


(CH) N CH, CH(OH)-CH COO

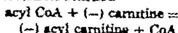
Although the presence of carnitine in various mammalian tissues has been well established for a relatively long time, its physiological and biochemical functions are still being elucidated. L-(-)-carnitine is particularly abundant in muscle. In 1959 Fritz showed that carnitine had a fundamental effect on the oxidation of free fatty acids by liver tissue. He proposed that carnitine could increase long-chain fatty acid metabolism by facilitating transport of the fatty acid to the sites of oxidation in the mitochondria. Specifically Fritz, Kaplan, and Yue[14] showed that the oxidation of long-chain fatty acid, the major metabolic fuel of the heart, is very highly dependent on the presence of carnitine.

I. Carnitine and intracellular fatty acid transport

Carnitine and fatty acyl transferring systems **(Fig. 1)**. How does carnitine act on fatty acid metabolism? Fatty acids taken up by the heart must first be activated to fatty acyl CoA before their further metabolism. In the heart, the major fate of fatty acid taken up is oxidation, which must occur within the mitochondrial matrix. Thus acyl CoA must penetrate the inner mitochondrial membrane which is normally impermeable to acyl CoA and to carnitine but not to acyl carnitine.

Carnitine can combine with activated long chain fatty acid to form *fatty acyl carnitine* which crosses the mitochondrial membrane. Despite extensive research it is not yet clear exactly how acyl carnitine formation promotes fatty acid transport, as seen by the number of schemes put forward to explain the role of carnitine in fatty acid oxidation.

The enzyme carnitine acyl transferase† catalyzes the reversible reaction


acyl CoA + (−) carnitine ⇌
(−) acyl carnitine + CoA

Acyl carnitine can pass the mitochondrial barrier probably the mitochondrial inner membrane, to liberate acyl CoA within the mitochondrial

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Abbreviations used: acyl CoA = long-chain acyl CoA esters = fatty acyl CoA; palmityl CoA = palmitoyl CoA; FFA = free fatty acids; carnitine acyl transferase = activity of all long-chain acyl transferases including carnitine palmityl (= palmitoyl) transferase.

†(carnitine transferase = carnitine acyl-transferase = acyl CoA-carnitine O-acyl-transferase).

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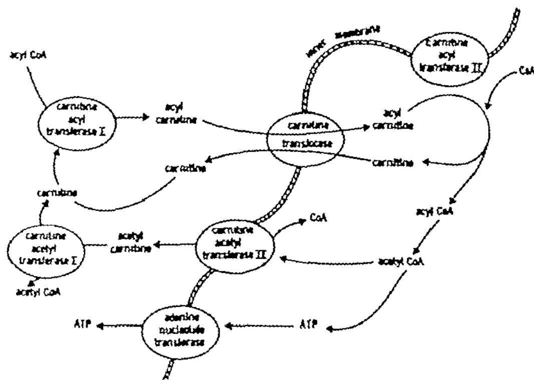
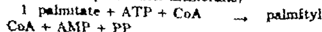


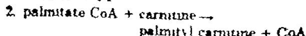
Fig. 1 Scheme to show steps thought t be required to transport extramitochondrial acyl CoA to within the mitochondrion. The inner membrane represents the permeability barrier The inner mitochondrial enzymes are carnitine acyl transferase II (Kopec and Fritz[illegible]), carnitine translocase (= carnitine acyl carnitine translocase, see Pande[illegible]), carnitine acetyl transferase II and adenine nucleotide transferase. Such enzymes are required in transporting acyl carnitine inwards and carnitine, acetyl carnitine, and ATP outwards. The enzymes carnitine acyl transferase I (Hoppel and Tomec[illegible]) and carnitine acetyl transferase I are held to be located on the outer part of the inner-mitochondrial membrane. The two carnitine acyl transferases may be in close physical opposition to the carnitine translocase For more details of operation of these cycles, see text. Note that the evidence for ts carnitine acetyl transferases is disputed.[illegible]

matrix where β-oxidation occurs.[illegible] Thus the basic scheme is as follows, taking palmitate as an example

Site A Site of fatty acid activation (mitochondrial cristae space outer membrane)



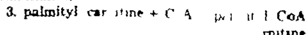
1 palmitate + ATP + CoA $\rightarrow$ palmityl CoA + AMP + PP



2. palmitate CoA + carnitine $\rightarrow$ palmityl carnitine + CoA

There is a barrier to the passage of palmityl CoA but not to palmit l carnitine between site A and B

Site B Site of fatty a l xidati n (mitochondrial matrix)



3. palmityl car itine + C A pal it l CoA rnitine

4. palmityl CoA β oxid t l CoA

Carnitine acyl transf r se could to the above scheme, be loc ed on t f the inner mitochondrial m n bra with

the finding of two separate enzymes by Kopec and Fritz[illegible] and by others.[illegible]

Carnitine translocase system The scheme developed by Ramsay and Tubbs[illegible] requires the presence of carnitine within the mitochondrial matrix[illegible] and the existence of carnitine-acyl carnitine exchange carrier (the carnitine acyl carnitine translocase of Pande[illegible]) The carrier acts by exchange diffusion and exports carnitine to the outer carnitine acyl transferase while transporting acyl carnitine to the inner carnitine acyl transferase.[illegible] However other groups have failed to find a dual distribution of carnitine acyl transferase in mitochondrial sub-fractions.

Furthermore, different authors give varying values for the carnitine content of heart mitochondria. Neely's group[illegible] have failed to find carnitine within rat heart mitochondria, and they originally postulated another scheme whereby carnitine travels between the outer and inner

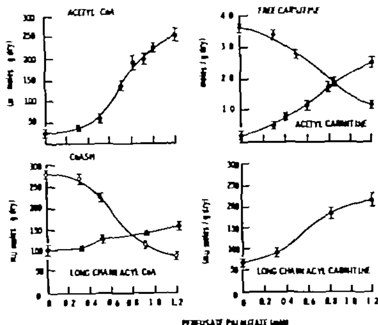


Fig. 2. Effect of increasing circulating FFA concentrations on intermediates of lipid metabolism in isolated Langendorff-perfused rat heart.[36] The normal physiological FFA concentration is about 0.4 to 0.8 mM. As the exogenous FFA increases, the tissue long-chain acyl CoA increases but there is a much more marked increase in long-chain acyl carnitine and acetyl CoA, indicating conversion of acyl CoA ultimately to acetyl CoA which is intra-mitochondrial. A major rise in the level of acetyl carnitine is explained by conversion of excess acetyl CoA to acetyl carnitine, and the accumulation of acetyl carnitine is matched by fall of tissue carnitine. Decreased availability of free CoA may reduce fatty acid activation and thereby limit fatty acid uptake which does not increase when external FFA was increased from 0.6 to 1.2 mM. The activity of carnitine acetyl transferase I must be limited by CoA lack, otherwise carnitine would be formed from acetyl carnitine. Data from Oram and associates[36] by permission of authors and of the *Journal of Biological Chemistry*.

carnitine acyl transferase systems (carnitine transferase I and II of Kopek and Fritz[39] or carnitine transferase A and B of Hoppel and Tomec[40]) without actually entering the mitochondrial matrix.[38] However more recently Neely's group appear to have accepted the data requiring intramitochondrial carnitine.[12] Thus, *Marquis and Fritz[41] found that mitochondria* contained 6 per cent of the tissue carnitine, similar to the value of 10 per cent found by Ramsay and Tubbs.[22] Pande[28] found 2 nmol. carnitine/mg. protein of rat heart mitochondria, the carnitine could be released by freeze–thawing. Only 19 per cent of the intracellular water is not in the cytosolic space[77] therefore, the localization of even a small percentage of the total myocardial carnitine in the mitochondrial matrix space could indicate a relative high concentration of carnitine. Whether or not carnitine is actually located in the matrix space does not affect the conclusion that at high rates of oxidation phosphorylation in the heart, the oxidation of long-chain acyl carnitine is limited by the activity of the inner carnitine transferase in translocating acyl units across the inner mitochondrial membrane.[38] Reduced levels of carnitine and CoA in the extra matrix space could limit the activity of *carnitine acyl* transferase activity.[38] A carnitine concentration of about 1.5 mM is required for maximal rates of oxidation of acyl CoA by isolated rat heart mitochondria.[28] Oram and colleagues[36] found that the whole tissue carnitine decreased from about 0.7 μmole/g. fresh wt to 0.2 to 0.3 μmole/g. as the perfusate palmitate concentration rose from 0 to 1.4 mM bound to albumin 3 g./100 ml. Alt the tissue content of long-chain acyl rose, most of the decrease in accounted for by an

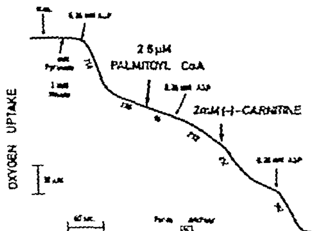


Fig. 3. Polygraphic recording of mitochondrial oxygen uptake.[44] Addition of mitochondria (mito) followed by substrates (pyruvate and malate) followed by ADP results in brisk O_2 uptake (steep fall of trace; 714 nanoatoms of oxygen per minute per mg of mitochondrial protein). As ADP is used up, respiration decreases (158 units). After addition of acyl CoA as palmitoyl CoA, addition of ADP stimulates respiration only slightly (212 units) until the addition of carnitine increases respiration (422 units) and further addition of ADP now gives rise to brisk respiration (562 units). Acyl CoA inhibits up to 94 per cent of the mitochondrial O_2 uptake. Thus carnitine, by converting acyl CoA to acyl carnitine (Fig. 1) reduces the acyl CoA inhibition. In the whole heart, an ischemia-induced carnitine deficiency could occur.[46] Data from Panda and Blanchaer by permission of the authors and the *Journal of Biological Chemistry*.

acetyl carnitine, which focuses attention on the carnitine acetyl transferase systems.

Carnitine and acetyl transferases (Fig. 2). Carnitine also participates in enzyme systems transferring acet l groups across the mitochon drial membranes. The enzyme carnitine acetyl transferase catal zes the reaction

acet l CoA + carnitine acetyl
carnitine + CoA

The activit of the acet l transferase declines with growing chain length from C[?] onwards, whereas the acti it of the ac l transferase decreases with decreasing hain length from C16 downwards.

The ratio of acet l arn tin t acetyl CoA is very high in the hear [illegible] Pearson and Tubbs[?] suggest that [illegible] rn tine acts as an acetyl CoA buffer ju [illegible] eatine phosphate buffers change in car [illegible] ATP supp rting evidence for this point [illegible] that t reac tants of the carnitine ac [illegible] r t rase tem remain near equilibrium during a wide range of changes in the reactants.

Neely and co-workers[?] suggest the following function for the carnitine acetyl transferases. Acetyl CoA produced within the mitochondria, *for example from β-oxidation, is either oxidized or* leaves the matrix space by becoming acetyl carnitine under the influence of carnitine acetyl transferase located in the inner mitochondrial membrane; this mitochondrial membrane is permeable to acetyl carnitine which again forms carnitine and acetyl CoA at the outer mitochondrial membrane, catalyzed by another carnitine acetyl transferase[?] and with the consumption of cytosolic CoA. *It should be noted that Edwards and associates*[?] could find only one type of carnitine acetyl transferase.

Thus "excess" intramitochondrial acetyl CoA, produced by "excess" uptake of FFA and maximal rates of transfer of acyl carnitine into the mitochondria, can "turn-off" FFA activation by lowering the extramitochondrial CoA content and thereby decreasing FFA activation and also *FFA uptake by the heart. Conversely at the start* of a work jump, the sudden increase of citrate synthase activity decreases mitochondrial acetyl CoA. The above series of events is reversed, and FFA activation is increased.[?] Thus the carnitine acetyl transferases are thought to couple extra mitochondrial uptake and activation of fatty acid to intra mitochondrial fatty acid oxidation.

Bode and Klingenberg[?] postulated that the activity *of the acetyl transferase* would be coupled to a transacylation reaction as follows.

acetyl carnitine + palmitate ⇌ palmityl
carnitine + acetate

Such a transacyl transferase system would allow regulation of CoA levels within and without the inner mitochondrial membrane. Fritz and Yue[?] were, however *unable to show significant activity* of this enzyme in the heart.

Carnitine, glycolysis and acetyl CoA/CoA ratios. Carnitine may indirectly help regulate the rate of glycolysis by increasing the activity of pyruvate dehydrogenase.[?] The mechanism could be an effect on the acetyl transferases. Thus, an *increased ratio of added carnitine to acetyl carnitine increased the mitochondrial ratio of CoA to acetyl CoA as a result of the activity of carnitine* acetyl transferase.[?] The increased CoA/acetyl CoA ratio activated pyruvate dehydrogenase.[?]

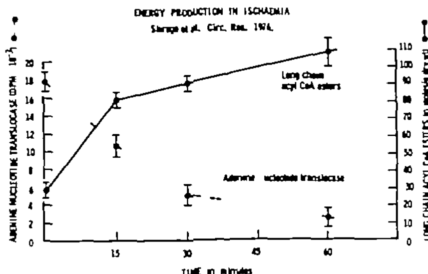


Fig. 4. Effect of duration of regional ischemia *(time in minutes)* on tissue contents of acyl CoA *(long-chain acyl CoA esters)* and activity of adenine nucleotide translocase. Note that as tissue content of acyl CoA rises so adenine nucleotide translocase activity falls (see also *Figs. 3* and *5*). Data from Shrago and colleagues by permission of the authors and the *American Heart Association, Inc.*

which could in turn accelerate the rate of glycolysis. Another link between carnitine and activity of pyruvate dehydrogenase is suggested by Shrago and co-workers. If carnitine deficiency leads to an accumulation of acyl CoA, then the intramitochondrial ATP/ADP ratio would rise, with inactivation of pyruvate dehydrogenase.

If the CoA/acetyl CoA ratio helps to regulate pyruvate dehydrogenase, then the postulated role of the acetyl carnitine transferase system in helping to regulate the mitochondrial CoA/acetyl CoA ratio may be of importance in the control of the relative contributions of glycolysis and of fatty acids to myocardial substrate metabolism.

Carnitine transferase systems. Effect of length of fatty acid chain. Carnitine, therefore, appears to function in the transferring systems both for the long-chain free fatty acid and for very short chains such as the acetyl moiety. However the carnitine carrier systems are obligatory for the oxidation only of long-chain fatty acids. A medium chain fatty acid can enter the mitochondria without the participation of carnitine, although the carnitine carrier systems can facilitate the transfer of medium chain acyl CoA derivatives at a rate of about 50 per cent of that of long chains. The rates of mitochondrial oxidation of extra long-chain or unusually unsaturated fatty acids are reduced because the rate of acyl CoA dehydrogenation may be rate-limiting.

Carnitine esters of erucic acid (C22.1) are more slowly oxidized than palmityl carnitine by heart mitochondria, and also inhibit oxidation of palmityl carnitine. The β-oxidation system may more readily become rate-limiting in the case of the CoA esters of the long-chain fatty acids of unusual structure. During feeding with erucic acid, triglyceride may accumulate because of the low rates of β-oxidation of the unphysiological fatty acids. Thus the chain length specific of carnitine transferase may play a role in erucic acid toxicity

Oxidation versus triglyceride formation. The major eventual fates of acyl CoA are oxidation or triglyceride formation and there is competition between these pathways. In certain circumstances, increased provision of α glycerophosphate, normally derived from glycolysis, may increase triglyceride formation; the explanation may be that α glycerophosphate can act as a trap for acyl CoA because glycerophosphate acyl transferase has a lower Km for acyl CoA than has the carnitine acyl transferase. Another mechanism increasing triglyceride synthesis may be a relative deficiency of carnitine for transport of acyl CoA into the mitochondria (see Ref. 38). Thus in the ischemic myocardium two factors help to increase triglyceride synthesis: increased α-glycerophosphate derived from accelerated glycolysis, and a carnitine deficiency (see below).

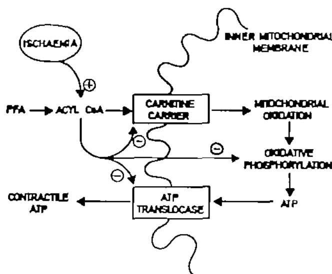


Fig. 5. Effect on ischemic metabolism of acyl CoA. The carnitine-dependent entry of acyl CoA into the mitochondrial matrix space, *shown in Fig. 1* is here schematically indicated as the *carnitine-carrier*. The prime defect in ischemia is defective mitochondrial β-oxidation, as result of which acyl CoA accumulates, probably initially within the mitochondria,[33] but because the carnitine carrier" system is freely reversible[34] extra-mitochondrial acyl CoA will also accumulate. Acyl CoA is highly specific inhibitor of adenine nucleotide transferase *(Fig. 3)*. Acyl CoA also has less specific effect on part of the carnitine carrier system (i.e., carnitine acyl transferase, *see Fig. 1*) by inhibiting the affinity for carnitine[35]; ischemia also directly depresses the acyl transferase activity.[36] Acyl CoA also inhibits β-oxidation,[37, 38] probably by non-specific effect. Of these effects, that on the adenine nucleotide translocase is most specific and probably of greatest clinical importance.

Because there is also evidence for increased breakdown of triglyceride, a "triglyceride-fatty acid cycle" has been thought to develop in the infarcting myocardium. If so, this cycle could account for ATP wastage and proton production.[39] Accordingly the reduction of the activity of this cycle would be one speculative mechanism whereby carnitine could exert beneficial effects in ischemia.

Acyl CoA and myocardial nucleotide translocase (Fig 3) Recent evidence shows that acyl CoA can reversibly inhibit the adenine nucleotide translocase of the heart. The cristae space is separated from the inner matrix space by the inner mitochondrial membrane whose properties include impermeability to adenine nucleotides,[34] CoA, acetyl CoA carnitine acetyl carnitine and (probably) acyl carnitin. Klingenberg and colleagues[44-46] proposed that endogenous nucleotides in the mitochondrial matrix space could be exchanged with nucleotides in the cristae space by a swing-door mechanism" involving the translocase, whereby one mole of ATP can be exchanged for one molecule of ADP by a mobile carrier system. Hence nucleotides could exchange relatively freely between the cristae space and the extramitochondrial space. By controlling entry of ADP into the mitochondrial matrix the rate of oxidative phosphorylation can be regulated by the adenine nucleotide translocase.

Several groups have shown that the addition of acyl CoA to isolated heart mitochondria inhibited nucleotide exchange,[14, 33, 47-49] and Pande and Blanchaer[47] found that further addition of carnitine could reverse the acyl CoA induced inhibition (Fig. 3)

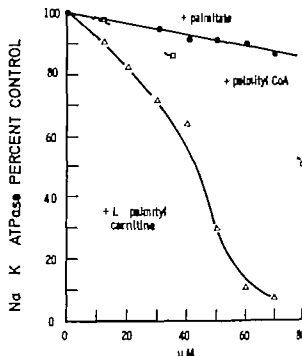


Fig 6. Comparative inhibitory effects of free fatty acid as palmitate, acyl CoA as palmityl CoA, and acyl carnitine as palmityl carnitine on Na /K ATPase of heart. Note much more marked inhibition of acyl carnitine than by acyl CoA. Data from Wood and associates[6] by permission of the authors and *Academic Press*.

Hence conditions increasing myocardial acyl CoA appear to be of importance in the regulation of the energy metabolism of the heart. Such conditions include those associated with a high circulating FFA concentration[33] such as the starved state and alloxan diabetes the accumulation of acyl CoA in alloxan diabetes is reversed by pretreatment with insulin. In starvation, acyl carnitine as well as acyl CoA rises.[1, 43]

Intracellular fatty acid transport. Conclusions

Carnitine is required for normal fatty acid metabolism to proceed via the transformation of acyl CoA to acyl carnitine. The formation of acyl carnitine *is thought to take place at an outer* mitochondrial membrane under the influence of carnitine acyl transferase I acyl carnitine is transported inwards by the carnitine–acyl carnitine translocase of Pande through the inner mitochondrial membrane to reach the sites for oxidation. The inner carnitine acyl transferase II liberates intra mitochondrial acyl CoA which undergoes β-oxidation, while intra mitochondrial carnitine is exported outwards by the carnitine translocase to re-enter in the above cycle. The system can be overloaded with accumulation of acyl CoA by excess circulating FFA. Acyl CoA is a specific inhibitor of energy transfer in and out of the mitochondria by the adenine nucleotide translocase situated on the inner mitochondrial membrane.

II Altered lipid metabolism in ischemia

Acyl CoA in ischemia (Figs. 4 and 5) The acyl CoA content of the heart is, at the most, doubled by the above conditions and by mild global ischemia,[p] whereas regional ischemia following coronary artery ligation may increase the content about *four* times.[13] The *Ki of the adenine nucleotide* transport system for acyl CoA is very low being only about 0.15 μM in isolated mitochondria,[14] but this should be compared with over-all tissue values of about 0.02 μM in non working *hearts perfused with glucose.*[3a] The *over-all* tissue content rises 1.5-fold in hearts perfused with high circulating free fatty acid concentrations.[14] Nevertheless, adsorption of acyl CoA to the mitochondrial membrane makes it difficult to correlate inhibitory concentrations and tissue values.[47] Recently Shug et al[13] and Shrago and co-workers[4] have shown that an accumulation of acyl CoA can be linked to impaired adenine translocase activity in the ischemic myocardium (Fig. 4) It follows that impaired mitochondrial energy production during myocardial utilization of fatty acids might be an important cause of myocardial damage in ischemia (Fig. 5)

A hypothesis has been proposed whereby conditions promoting acyl CoA formation promote metabolic damage to mitochondria and hence exaggerate ischemic damage.[13, 47, 48] Acyl CoA accumulation could inhibit the formation of ATP because extra mitochondrial ADP is transported inwards at a reduced rate, while intra mitochondrial ATP already formed is transported outwards at a reduced rate.[47] Hence the whole *mitochondrial energy production mechanism is* impeded which is of critical importance because mitochondrial energy production remains a major source of ATP even in the infarcting myocardium, provided that there is a residual collateral blood supply[42]

There are at present two possible criticisms of the acyl CoA hypothesis. First, acyl CoA should accumulate *within* the mitochondria in ischemic tissue[43] if the scheme involving carnitine translocase is correct (see above) whereas the studies showing a depressant effect of acyl CoA on mitochondrial function have utilized *externally added* acyl CoA. However Klingenberg and colleagues[44, 46] argue that an inhibitor of adenine nucleotide translocase added either internally or externally could be expected to paralyze the mobile carrier system equally effectively Some recent direct evidence also suggests that internal acyl CoA also inhibits the ATP–ADP translocase.[47] Secondly a puzzling feature of the observations of Shug and associates[13] is the large accumulation of acyl CoA in the non-ischemic area in which the content of acyl CoA was *indistinguishable from that in the ischemic tissue,* although adenine nucleotide transferase activity was more than twice as high in non ischemic tissue. A possible reconciling explanation is that normal mitochondrial energetics are required for *ATP ADP* exchange in the required direction,[47] and thus it is the combined effects of depletion of tissue high-energy phosphate compounds and of acyl CoA accumulation which inhibit translocase activity

However the above criticisms suggest that other effects of acyl CoA and effects of related compounds such as acyl carnitine and tissue-free fatty acid should also be evaluated.

Other effects of acyl CoA. Acyl CoA may also act at sites other than the carnitine acyl transferase system

1. High concentrations of acyl CoA inhibit its own oxidation.[48]

2. Long-chain acyl CoA is a potent reversible inhibitor of carnitine acetyl transferase, competing with acetyl CoA the enzyme used was from pigeon breast muscle, which is a red muscle with metabolic similarities to heart.[49] Thus accumula

tion of acyl CoA may be a factor increasing the *acetyl CoA levels during perfusion with excess* fatty acid[14]; however during ischemia acetyl CoA decreases as acyl CoA rises.[44]

3. The tricarboxylate carrier mitochondrial system is sensitive to acyl CoA in rat liver mitochondria, suggesting that acyl CoA can regulate gluconeogenesis and lipogenesis via this mitochondrial carrier system.[46] However the tricarboxylate carrier is absent or low in the heart and gluconeogenesis does not occur

4. Acyl CoA can inhibit the transport of phosphoenolpyruvate into heart mitochondria by the adenine nucleotide translocase, such transport is coupled with Ca egress. Carnitine, by removing acyl CoA allows phosphoenolpyruvate-induced Ca egress to occur.[47] The physiological meaning of these findings is not yet clear although mitochondrial Ca exchange may play a role in regulation of cytosolic Ca and cardiac contraction.[48]

5. Wood and colleagues have recently reported that the K /Na membrane ATPase is inhibited by acyl CoA, thereby possibly explaining K loss from the acutely ischemic myocardium.

6. Acyl CoA can inhibit (Ki = 5 μM) the fatty activating enzyme, fatty acyl CoA synthetase, thereby limiting fatty acid activation when acyl CoA accumulates as during perfusion with a high medium fatty acid concentration.

7. Acyl CoA stimulates the acylation of α glycerophosphate and hence, glyceride formation.

8. Finally acyl CoA inhibits malate dehydrogenase especially in the direction of oxaloacetate to malate which might have a physiological role

Acyl carnitine (Fig 8) Whereas acyl CoA rises only by about one and a half times during perfusions with high xogenous FFA long-chain acyl carnitine increased by n arly four fold[14] Similarly during wh le h art ischemia acyl CoA rises two-fold but acyl carnitin by nearly four fold. The question arises f th possible inhibitory effects of acyl carnitine whi h considerably more powerful inhibit r t the a t it of bovine heart Na, K ATPase th t A (Fig 8) However acyl carnitin did n t hibit the adenine translocase activit f h t mit hondria.

Free fatty acid effects. Initially Kurien and Oliver[1] stressed the role of an accumulation of free fatty acid in ischemic tissue in their hypothesis, linking increased circulating free fatty acids and arrhythmias. The failure of Regan and associates[75] to find any increase in tissue FFA in regional ischemia argued against the hypothesis, but more recently Bing's group[76] have performed lipid analyses by gas chromatography and showed increased tissue contents of palmitate, stearate, and oleate in regional ischemia. Using an isolated rat heart model of combined oxygen and substrate depletion, Lochner and co-workers[77, 78] could link an increased tissue (but not mitochondrial) FFA content to impaired mitochondrial function. These recent data appear to link fatty acid-induced alterations of mitochondrial function to impaired lipid metabolism in ischemia. However the effect of addition of albumin in improving function of damaged mitochondria[79] cannot simply be removal of free fatty acids from the mitochondria, because the mitochondrial content of free fatty acids was not increased.[77, 78] Because the model of Lochner and colleagues[78] is not directly applicable to true low flow ischemia, it would be of considerable interest to repeat her findings in true regional ischemia.

Atractyloside and ischemic injury Mitochondrial adenine nucleotide translocase activity can be inhibited by atractyloside.[44] Shug and associates[80] infused this relatively specific inhibitor into the left anterior descending coronary artery of the dog (75 μMole atractyloside per minute) and found decreased tissue ATP and creatine phosphate together with decreased adenine nucleotide translocase activity and elevation of the ST-segment in the epicardial electrocardiograms. Isolated mitochondria from the ischemic zone showed depressed respiration. In areas not directly perfused by atractyloside, mitochondrial respiration was also inhibited and the inhibition was reversed by carnitine but not so the mitochondria from the atractyloside-infused zone which were resistant to carnitine. A possible explanation for these phenomena may be that inhibition of the adenine translocase can not be overcome by carnitine but the the ischemia induced change in the non ischemic zone (probably acyl CoA accumulation) is reversible by carnitine (see Section III).

Lipid metabolism in ischemia Conclusions

Accumulation of tissue acyl CoA in ischemia is an attractive hypothesis to explain the lipid induced impairment of mitochondrial function found in ischemia and the effect of atractyloside in producing ischemic injury Certain incongruities in the data presently available suggest alternate or additional roles of the harmful effects of other lipid intermediates, such as acyl carnitine or free fatty acids themselves or even effects of acyl CoA other than those on the adenine nucleotide translocase.

III Carnitine and ischemia

The question arises as to whether carnitine availability is ever likely to be limiting in ischemia, and/or whether provision of carnitine could accelerate removal of acyl CoA and thereby improve ischemia. To show that carnitine could play a role in decreasing myocardial ischemic damage, and ultimately infarct size, would require a knowledge of four postulates. First, tissue carnitine levels in the ischemic tissue must be known. Secondly the Km for carnitine in the acyl CoA transferase system should be such that the amount of decrease could be significant. Thirdly carnitine would have to be taken up by the ischemic tissue if there were an adequate collateral circulation as in the dog. Fourthly rates of oxidation of long-chain fatty acid should be increased and over-all tissue ATP should increase after provision of carnitine to the ischemic heart.

Present information on the above postulates is as follows. First, Shug and colleagues[33] have recently shown that the myocardial carnitine content decreases by one-third after 10 minutes of regional ischemia and by 30 minutes the content is reduced to about 50 percent acetyl carnitine and long-chain acyl carnitine increase in content. Secondly the maximal oxidation of acyl CoA by rat heart mitochondria is achieved by a carnitine concentration of 1.5 mM,[34] not far off the tissue value of about 1.0 μMole/g wet weight.[35] Hence a fall of tissue carnitine by half in ischemia[36] should significantly reduce oxidation of acyl CoA. Thirdly infusion of L-carnitine into the coronary bed during regional ischemia in the dog[4] was associated with a local increase in carnitine content to 2.2 μMole/g weight (but the ischemic value without infusion was not given). Fourthly the infusion of L-carnitine increased tissue ATP creatine phosphate, and adenine nucleotide translocase activity in ischemic tissue.[11] Furthermore after carnitine addition directly to ischemic heart mitochondria, there was partial restoration of the depressed oxygen uptake[11] and carnitine increased the oxygen uptake of heart mitochondria after inhibition by acyl CoA.[13]

Further information of the role of carnitine in ischemia might be obtained by decanoyl carnitine which inhibits long-chain acyl carnitine transferase in the isolated perfused liver and thereby blocks fatty acid oxidation.[12] Decanoyl carnitine should, therefore, lead to accelerated accumulation of acyl CoA in the ischemic heart which should further aggravate ischemia if the acyl CoA ischemia hypothesis be correct.

Other relevant effects of carnitine in ischemia Preliminary work suggests that pretreatment with carnitine also reduces the degree of ST segment elevation following coronary flow reduction in the dog.[42] The absence of an effect of carnitine in decreasing mitochondrial damage in substrate-free, hypoxic perfused hearts does not rule out an effect of carnitine in ischemia, because of the major metabolic differences between anoxia and ischemia.[11] Carnitine also has some antiarrhythmic properties, as shown by an effect sometimes similar to that of quinidine when tested against electrically induced atrial fibrillation.

The improvements reported to follow the administration of carnitine to dogs with developing infarction may conceivably arise on the basis of effects of carnitine not involving changes in cardiac fatty acid metabolism. One possibility is that carnitine could activate pyruvate dehydrogenase by improving myocardial energy metabolism[43] and thereby decrease ischemic damage.[44, 45] If carnitine had an effect on the circulating free fatty acids, that might alter the outcome of myocardial ischemia. At present, no hard data exist to exclude a possible antilipolytic effect of carnitine as suggested by Kader and colleagues.[46] Furthermore, carnitine may not only decrease palmitate uptake by the perfused rat heart but also increase incorporation of labeled palmitate into phospholipid and triglyceride while decreasing incorporation into tissue fatty acids.

Could some of the reported effects of carnitine be the reflection of any property of carnitine quite removed from effects on fatty acid metabo-

lism? One possibility is the acetyl choline-like activity of carnitine and especially of acetyl carnitine. Thus Riemersma and Oliver found a significant slowing of heart rate when they gave carnitine to dogs. However carnitine is many thousand times less potent than acetyl choline on the isolated frog rectus abdominis muscle and acetyl carnitine about 600 times less potent than acetyl choline, suggesting that the cholinergic properties of carnitine are probably not of major importance. More data on the heart rate during carnitine administration are required.

Thus the hypothesis that carnitine increases intracellular disposal of acyl CoA and thereby improves mitochondrial function appears most likely and warrants further experimental evaluation, but other mechanisms cannot yet be excluded. If increased tissue-free fatty acids rather than acyl CoA are the harmful factor in ischemia, then carnitine could act by removing acyl CoA and increased activation of fatty acids could then occur. Alternatively carnitine could decrease tissue-free fatty acids by promotion of glyceride formation.

Carnitine in angina pectoris. Direct evidence for a therapeutic role for carnitine in myocardial ischemia has been obtained in man. Patients with angina pectoris given DL-carnitine (20 to 40 mg./Kg.) could tolerate an increased duration of pacing and a greater pressure-rate product; myocardial lactate extraction and left ventricular end-diastolic pressure decreased. Thus DL-carnitine increased the resistance of the human heart to pacing induced ischemia, but the mechanism is not clear because carnitine is not lost from the dog heart during a short period of reversible ischemia.

Carnitine, acute diabetes, and myocardial ischemia. In acute alloxan diabetes, a relatively early finding was that carnitine content of peripheral muscle decreased and the body pool of carnitine was reduced. In[illegible]ulin treatment reverted these abnormalit[illegible] t[illegible] n[illegible]rmal. This finding led to a search f[illegible]r similar metabolic defects in diabetic hearts. The [illegible]nt[illegible] [illegible]f free carnitine in the heart falls in [illegible]ll[illegible]x[illegible]n diabetes. The free carnitine content of the r[illegible]t he[illegible]rt is also decreased by perfusion with fatt[illegible] a[illegible]ids ketones or pyruvate by conversion of [illegible]d[illegible]genous carnitine to acetyl carnitine.

Thus it is conceivable tha[illegible] [illegible]arnitin[illegible] d[illegible]fi[illegible]i[illegible]n[illegible]y may exist in acute ketotic di[illegible]tes, in whi[illegible]h heart tissue acyl CoA increases. More basic data need to be gathered about the cellular location of the carnitine deficiency and of the acyl CoA accumulation in the diabetic heart. If the cause of acyl CoA accumulation is simply provision of fatty acids at higher rates than can be oxidized, then carnitine may play a therapeutic role.

Recent data suggest that the heart from alloxan diabetic rats is more susceptible to myocardial ischemia than in the normal heart; an increased severity of coronary artery disease in diabetes is not involved in this experimental model. The arguments for assessment of carnitine therapy in ischemia in the non-diabetic heart would seem even stronger in the case of the diabetic heart.

Carnitine and ischemia: Conclusions

In experimental ischemia, tissue carnitine decreases and may become rate-limiting. Infusion of carnitine restores the defect and ameliorates some biochemical and electrocardiographic features of ischemia. In one study carnitine also relieved pacing induced angina. But the exact mode of action of carnitine depends on clarification of the possible roles of acyl CoA, acyl carnitine, and tissue-free fatty acid in producing the metabolic defects in ischemia.

IV. Carnitine and non-ischemic conditions

Heart failure. Wittels and Spann have shown that content of carnitine in the heart is decreased in homogenates from failing guinea pig hearts and that there is decreased oxidation of palmitate. Such effects need confirmation and warrant further biochemical work.

The neonatal heart. In the newborn rat heart there is a lower rate of oxidation of FFA as palmitate and of acyl CoA as palmityl CoA, with a lower activity of long-chain fatty acid CoA–carnitine transferase and a lower cardiac content of carnitine. These findings, if they can be extrapolated to the human neonatal heart, raise the possibility that some cases of neonatal heart failure may be related to deficient metabolic activity of carnitine and/or the carnitine transferase system.

Adriamycin cardiotoxicity. Carnitine is an effective agent against experimental arrhythmias produced by an anthracycline antineoplastic drug such as adriamycin. By inference, carnitine might also be effective in preventing the cardio-

myopathies induced by adriamycin and the closely related compound daunorubicin,[illegible] which can cause congestive heart failure.[67] There should now be investigations of the effects of adriamycin on carnitine and acyl CoA contents of the heart. In cultured heart cells, adriamycin stops rhythmic contraction, inhibits cell division of non-myocardial cells, and decreases the energy change, externally added creatine partially reverses the depression of creatine phosphate, suggesting that the actual regulation of energy production was not totally impaired.[illegible] However the effects of carnitine were not reported.

Empirical clinical trials with the use of carnitine to prevent adriamycin side effects would appear warranted, especially because of the growing importance of adriamycin as an antileukemic agent.

Diphtheritic myocarditis. There is a defect of lipid metabolism in diphtheria, characterised by impaired fatty acid oxidation, carnitine deficiency and accumulation of myocardial lipid.[illegible] Intraperitoneal administration of L-carnitine increased tissue carnitine and decreased the defective lipid oxidation in diphtheritic guinea pigs, while intravenous carnitine improved left ventricular function in dogs pretreated with diphtheria toxin.[illegible] While diphtheritic myocarditis is an uncommon cause of death in the West, there must still be a high incidence in many developing or underdeveloped countries. Therapeutic trials of carnitine would not only be warranted but should be encouraged. There is some evidence that L-carnitine is therapeutically more effective than DL-carnitine.[illegible]

V Conclusions

The mechanisms governing oxidation of free fatty acid (FFA) in the heart reveal a special role for carnitine. A major factor governing the rate of FFA metabolism is the rate of fatty acid transport into the mitochondria, which is in turn regulated by the carnitine acyl transferases and a carnitine–acyl carnitine translocase system. The latter transfers acyl CoA (activated intracellular FFA) into the mitochondria for β-oxidation while exporting carnitine from the mitochondria. During ischemia, acyl CoA accumulates and inhibits the activity of the ATP–ADP exchange system. Hence it is postulated that ischemia and the resultant acyl CoA accumulation impede mitochondrial synthesis and transfer of ATP to the cytoplasm when it is needed for contraction. However the roles of other fatty acid metabolites such as acyl carnitine and free fatty acid itself need evaluation and may explain some of the incongruities in the acyl CoA hypothesis.

The most convincing argument for the possible therapeutic use of carnitine would depend on the projected role of acyl CoA in impairing mitochondrial metabolism during ischemic damage. Should it be confirmed that provision of carnitine could reduce acyl CoA accumulation and thereby improve survival of ischemic tissue then the arguments for the vigorous assessment of carnitine as a therapeutic agent would become compelling. Prior animal experiments should be directed to confirmation of existing reports that there is a correctable deficiency of carnitine which develops in ischemia. Observations should include assessment of the possible side effects of carnitine such as the cholinergic and possible antilipolytic effects. Recent reports suggest that carnitine may decrease ST-segment elevation and induce metabolic improvement in experimental myocardial ischemia. In one study carnitine is also reported to benefit pacing induced angina. All such therapeutic implications would require additional rigorous experimental and laboratory investigation and, where indicated, further clinical trials. There is good evidence implicating carnitine deficiency in the development of experimental diphtheritic myocarditis. Hence evaluation of carnitine therapy would also appear warranted in the case of diphtheritic myocarditis and in adriamycin toxicity

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Addendum

Since preparing the manuscript, Neely's group[illegible] has shown that there is a marked accumulation of acyl CoA and of acyl carnitine in the mitochondria in an isolated rat heart model of global ischemia, and that the percentage of the total cellular carnitine associated with the mitochondria increased from under 10 per cent to over 25 per cent during ischemia, indicating a net transfer of carnitine from the cytosol to the mitochondrial matrix. While a deficiency of cytosolic carnitine developed, it would seem that in the rat heart model therapeutic provision of

carnitine cannot be expected to remove the accumulation of the intramitochondrial acyl CoA and acyl carnitine which may be contributing to the ischemic damage. A mode of action of carnitine not involving a primary metabolic effect remains possible and is rendered somewhat more likely by the finding that carnitine is an inotropic agent and can increase the coronary blood flow.[188] On the other hand, the Neely rat heart model may not be directly applicable to the situation in regional ischemia with developing myocardial infarction or there may be a species difference, and further observations on the action of added carnitine in other animal models of ischemia and in angina in patients are required.

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Drug management of hypercholesterolemia

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A discussion of the use of drugs for hypercholesterolemia should first emphasize that diet is the treatment of choice and drugs an adjunct. Prior to embarking on pharmacologic therapy a considerable effort should have been exerted to accomplish the dietary alteration appropriate to the lipid abnormality. This frequently rather fundamental change in life style usually requires that the physician collaborate with personnel specifically trained in nutritional counseling and the utilization of fairly extensive instructional methods and materials.

For the hypercholesterolemic patient not adequately responsive to diet, in whom evaluation of other risk factors justifies intervention, several drugs are approved for use in the U.S. These vary in their chemical nature and in their relative effects on the complex patterns of circulating lipoproteins.

This discussion will be focused primarily on data regarding drug effects on total cholesterol, a measurement which is generally available at a reasonable cost, and the level of which in most instances fairly accurately reflects the level of low density (beta) lipoproteins.

Beta-sitosterol

In 1937 Sperry and Bergman reported that liver cholesterol was reduced when mice were fed sitosterol. In 1951 Peterson and associates[1] reported that both mixed soybean sterols and β-sitosterol alone prevented hypercholesterolemia in chickens fed cholesterol. Pollak two years later confirmed that β-sitosterol had a cholesterol lowering effect in rabbits[2] and in man.

Beta-sitosterol is itself poorly absorbed but probably competes for sites of esterification of the structurally related cholesterol molecule in the intestinal wall, thus decreasing cholesterol absorption.[3-8] In a rare recently described lipid storage disease β-sitosterol may be significantly absorbed.[10]

Clinically a number of investigators have had success in lowering cholesterol levels by sitosterol administration.[11, 14] Beta-sitosterol derived from tall oil is available as a 20 per cent suspension and when administered in a dosage of 15 to 30 ml. three or four times daily with meals, usually reduces cholesterol (primarily beta or low density lipoprotein cholesterol) 10 to 15 per cent.

Side effects are minimal and include a mild laxative effect and occasionally abdominal distress. The inconvenience of the dosage form has probably contributed to a compliance problem and been a deterrent to wider use.

Nicotinic acid

Altschul, Hoffer and Stephen in 1955 probably speculating that high doses might increase oxidation in the tissues, evaluated injected nicotinic acid in rabbits for a possible cholesterol-lowering effect. They subsequently tested doses of one to three grams orally in human subjects and found decreases of serum cholesterol proportional to pretreatment levels, ranging from six to 21 per cent.[15]

Although widely used, the mechanism of the lowering effect of nicotinic acid on total cholesterol and low density lipoprotein cholesterol is still not clear.[16, 17]

Nicotinic acid is a potent inhibitor of the release of free fatty acids from adipose tissue,[18]

*Cytellin (Lilly).

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probably through a reduction in cyclic AMP on which triglyceride lipase is d pend nt. Limitation of the availability of free fatty acids for h patic synthesis of tri lyceride containing very low den ity lipoproteins could account for the dimi nution in this fraction noted after nic tinic acid. Since very low density lipoproteins are the major precursors of low density lipoprotein the observed decrease in LDL could be lar ely an indirect one through this mechanism. In addition, nicotinic acid may have a d se-dependent effect on enhancing very l w density lipoprotein catabolism. An occa ional patient in whom this drug produces a marked fall in very l w den ity lipopr teins may h w an in rease in low den ity lipoproteins. Some data indicate a direct chles ter l low ring eff ct thru h a decrease in synthesis. Reported tudies on fecal t rol excretion are conflicting.

Several clinical studie have c nfirmed the activity of ni otinic acid on serum lipids. The response rate to doses of 3 to 6 grams of nicotinic acid per day ha been reported to be per cent.

In the C r nary Drug Project the long t rm redu tion of h lester l was 10 per c nt of tri glycerid s 26 per c nt in the nic tinic acid group. No reduction in m rtality w observed but a signifi nt fav rable ffect occurred in regard to ecurr nt n n fatal myocardial infarcti n in mparison t th pla el ubject.

Flushing f th kin with r without para thesia, and pruritu urs with the ne essary d se f r hclest l l w ring in irtually ll patient and pers t in l t l pe nt. There is no gen r l g em t whether not l w initial dosag th se tin es a d y gradually incr a ing t l s g n l l decreases in id n of sid ll t t t tinal int l ran e arrhythm t n glu ose int l r ance an l l j ur a ad rse reactions.

Dextrothyroxin

Since hyperthy l lly associat l with low levels of t l l s l f thyroid like drug t l w h t r l b lsee appealing.

In 1955 Lerman and Pitt Rivers bse l that thyroacetic acid analogs f thyroxin l w ed cholesterol without increasing the basal m bolic rate. In 1960 Boyd and Oliver report positive clinical trials with dextrothyroxin an isomer which has only one-eighth to ne tenth the metabolic eff ct f the l form.

Dextrothyroxin incr ases cholesterol synthesis but also produ es an increase in fecal sterol and increased c nversion of ch lesterol to bile acids. This increase more than ffsets the increased synthesis. Maximum serum chole terol decr ases occur in one to two m nth the decrease is mainly in the low den ity fraction. Very l w d n ity lip pr t ins are not consistently af f ct d.

Several clinical tudies have c nfirmed the ch lesterol l wering effect of d thyr xin in man and hown a decrease in l w density lip proteins averaging about 20 per nt at a dosage of 4 to 8 mg/day. Incidence of an ina pect ris in patients with thi problem is not infrequ ntly increased at the high r dose levels.

The u ual tarting d se of d thyroxin is 1 to mg/day in adult 0. to 0.1 mg kil gram in children. Untoward ffe t mimic hyperthyroid i m. Impaired glucose tolerance and ugmenta tion f the effects f digitalis and oral anticoagulants have been r ported.

In the Coronary Drug Project d thyr xin was interrupted because f an increase in m rtality in that ub-group of patients who had a h tory of arrhythmia conduction defects angina pectoris, multiple infar ts or a higher than av ra dia tolic blood pressure.

The use of dextrothyroxin sh uld be limited to euthyroid ubjects who are hyper holest rolemic, without evid nce of ischemic heart d sease or un table rhythm and probably should be r stricted to young patients.

Clofibrate

Hellman and associates in 1962 report d that andr terone although having a lipid lo ering effect when giv n parenterally was ineffective orally and could not be given by injection because of local discomfort and occasional fev r. However wh n th y administered 20 to 30 mg of androsteron with l l l g of the branched chain fatty acid ester a para-chlorophenoxyisobutyrate f y m rith a redu tion in cholesterol and triglyc eride was n ted. Oliver in the same year also found this ombination active in lowering lipids and uric a id. H llman and colleagues in 1963 reported studies indicating that chlorophenoxy isobutyrate possessed all of the lipid lowering

effects and other properties earlier ascribed to the combination. The activity of clofibrate on blood lipids has been confirmed in many studies, and the drug has been extensively used for a period of more than ten years.

Clofibrate administered as the ethyl ester at a usual dose of 2 g/day in two or four divided doses is well absorbed and rapidly hydrolyzed to the acid which is highly bound to serum albumin. It has a half life in man of 10 to 12 hours and is excreted in the urine as the glucuronide.

The pharmacological actions ascribed to clofibrate are multiple and it is not clear which of these pertain to its observed actions in man. In a recent review of data on mechanisms, Yeshurun and Gotto suggest that a decrease in hepatic synthesis or release of triglycerides is the most likely relevant action.[34] Lewis points out that recent studies emphasize an enhanced uptake of very low density lipoprotein triglyceride. Both in the rat[12] and in man,[13] an inhibition of cholesterol synthesis has been demonstrated. Whether the effect of clofibrate on serum cholesterol is direct through synthesis inhibition, or indirect through a decrease in very low density lipoproteins, the major precursor of low density lipoproteins, is not clear. In some patients, especially those with markedly elevated pretreatment triglyceride levels, there may be an increase in LDL cholesterol during therapy with this drug.[41, 54] This elevation, which may well be deleterious, may not be reflected in the total cholesterol measurement. The published data on the possible effect of clofibrate on experimental models for atherosclerosis vary from no effects seen in one study of cholesterol fed chickens, rabbits, or monkeys,[55] little or no effect with 0.3 per cent in the diet of rabbits,[56, 57] to significant regression in size and sudanophilic staining and extent of calcification of lesions in swine.[58]

In controlled clinical studies designed to define efficacy three secondary prevention trials (administering the drug to patients with one or more previous myocardial infarctions) and one primary prevention trial (patients at risk for myocardial infarction but no previous episode) have been published.

Total mortality was significantly reduced in the Newcastle but not in the Scottish trial.[60] The rate of non fatal myocardial infarction was reduced in both studies but the reduction was not statistically significant. Benefit appeared to be confined to those sub-groups presenting with angina pectoris. There appeared to be little relationship to the initial cholesterol value or to the extent to which is was lowered. In the U.S., the Coronary Drug Project included 1 103 subjects in the clofibrate group, followed for a mean period of six years. Mean lowering of serum cholesterol was 6.5 per cent, triglyceride 21 per cent. No significant reduction in total or coronary mortality was observed when compared to the placebo group.[33] In a primary prevention trial,[61] clofibrate afforded protection from myocardial infarction not dependent on a significant lowering of serum lipids. In a prospective angiographic study [62] there was no significant influence on the rate of progression of coronary artery disease in a one-year period. In a study of early femoral atherosclerosis, utilizing computer densitometry as well as human film reading, regression of disease was limited to those patients who had shown a significant reduction in cholesterol, triglyceride, and blood pressure.[64]

Effects other than on lipids may be relevant to the observations in these clinical trials. Clofibrate has been reported to have a desirable effect on the clotting mechanism, either through action on the platelets or by decreasing fibrinogen.[65]

Clofibrate has a high degree of patient acceptance, a low incidence of side effects, most of which are limited to the gastrointestinal tract and are often transient. Other occasional problems associated with its use include skin rash, leukopenia, alopecia, weight gain, transient reversible abnormalities in liver function tests, and myositis. Because of its albumin binding, dosage requirements of coumadin-type anticoagulants may be reduced by as much as one-half.

A surprising finding in the Coronary Drug Project was a low but statistically significant incidence over placebo of thromboembolism, thrombophlebitis, angina pectoris, intermittent claudication, cardiac arrhythmias, and a twofold increase in the incidence of gallstones.[33]

In recently reported studies, with doses approximately eight times that used clinically both rats

Atromid-S (A [illegible])

In recently published report of WHO sponsored multi-centered European trial, clofibrate produced 9 per cent mean decrease in cholesterol and as associated with 25 per cent reduction in ischemic heart disease morbidity but no reduction in mortality

and more developed non invasive hepatic tumors with long term administration.[?] No comparable lesions have been reported in other species or in man.

Bile acid binding resins

Cholestyramine. In 1961 Siperstein, Nichols, and Chaikoff[?] reported that the plasma cholesterol increase observed in force-fed cockerels could be inhibited by simultaneous feeding of 3 per cent ferric chloride. The mechanism was thought to be a precipitation of bile acids in the intestinal lumen and interference with reabsorption. These authors suggested that binding of bile acids by some less toxic agent might serve as a means of controlling atherosclerosis.

In 1960 Tennent and associates[?] reported that feeding a high molecular weight bile acid binding polymer did interfere with aortic plaque formation in cholesterol fed cockerels, lowered cholesterol in normal cholesterolemic cockerels and dogs and increased fecal sterol and bile acid excretion in the dog. A basic anion exchange resin containing quarternary ammonium groups attached to a styrene [illegible] per cent divinyl benzene skeleton was chosen for further studies. This polymer was found to be well tolerated in chronic feeding studies in dogs, and was effective in lowering cholesterol over a range of 0.05 to 1 per cent in the diet. Bergen and colleagues* were the first to publish on the efficacy of this resin in man. Clinical studies by many investigators have established that bile acid binding resins offer the greatest potency of any of the available cholesterol lowering drugs with decreases as great as 50 per cent being reported in some subjects. Mean reduction [illegible] sity lipoprotein cholesterol in various studies h[illegible] ng d from 27 per cent to 40 p[illegible] A[illegible] nent or occasionally persisting in[illegible] w[illegible] nsity lipoprotein triglycerid[illegible] h[illegible]

Cholestyr[illegible] n indigestible non-absorbable [illegible] the recommended dosage [illegible] n rease bile acid excretion [illegible] g [illegible] hours (approximately [illegible] mult. The decreased concentra[illegible] g [illegible] an increased hepatic con[illegible] bile acids. The rate of [illegible] lensity lipoproteins is accelerated without an increase in low density lipoprotein synthesis.

That tissue pools may contribute to the cholesterol converted to bile acids is suggested by the clinical observations of decreasing size of xanthomas in patients receiving cholestyramine.

Wissler and Vesselinovitch have evaluated cholestyramine in a well-established primate model for the study of regression of advanced atherosclerosis. Their experiment involved feeding Rhesus monkeys an atherogenic diet for 12 months, at which time well-developed coronary and aortic lesions are demonstrable. Groups of animals were continued on an atherogenic, or low fat low cholesterol diet, with or without cholestyramine at a dosage of approximately 6 grams per monkey per day for an additional 12 months. Substantial regression (by about 50 per cent) of aortic and coronary lesions occurred during the second year of observation when cholestyramine was administered concurrently with a continuing atherogenic diet. Even greater regression was seen when cholestyramine was given in conjunction with a low fat-low cholesterol diet.

On the basis of its promise as a possibly effective means of altering the atherosclerotic process, a 12-center primary prevention trial of cholestyramine was funded in 1975 projected to involve 4,000 hypercholesterolemic male volunteers aged 35 to 59. Subjects have been recruited and randomly assigned to a cholesterol lowering diet plus placebo or a diet plus cholestyramine. It is planned to follow these individuals for seven years.

Colestipol. Recently a second bile acid binding resin, colestipol, has been added to the U.S. market. This is an insoluble high molecular weight basic anion exchange copolymer of diethylene-triamine and 1-chloro-2,3-epoxypropane. It is thought to have an action identical to that of cholestyramine—binding bile acids in the intestine forming an unabsorbed complex that is excreted in the feces. Goodman and co-workers in 1973 reported an average decrease in cholesterol of 21 per cent on subjects receiving 15 g/day. The effectiveness of colestipol as a cholesterol lowering agent has been confirmed in many clinical studies.[?]

A recently published study by Dorr and asso-

*Questran (Mead-Johnson).

†Colestid (Upjohn).

ciates[illegible] involved 2,278 hypercholesterolemic subjects randomized to colestipol or placebo, and observed over periods ranging from one to three years. Dosage of colestipol was 5 grams mixed with water juice, milk or similar liquid, three times daily just before meals. At one month the average decrease in serum cholesterol was 32 mg./dl. for the treated group, and 7 mg./dl. for the placebo group In those patients receiving medication for three years, an average decrease in cholesterol of 42 mg./dl. was observed, for placebo the decrease was 14 mg./dl.

Mortality attributable to coronary heart disease was significantly lower in the colestipol treated than in the placebo group. Both total and coronary mortality was apparently decreased in those with evidence of coronary heart disease on entry A significant difference between drug and placebo on total mortality in men was observed only in those under age 50 at entry The mortality rate of the women included in the study (most of whom were post-menopausal) was not affected. The withdrawal rate was 16 per cent in the first three months and 38 per cent over all. This study has been criticized[illegible] for combining a primary and secondary prevention trial, for the high drop-out rate, and for other deficiencies, some of which are unavoidable in studies of this type.

Adverse effects of bile acid binding resins are most commonly nausea, constipation, and exacerbation of hemorrhoids. Theoretically deficiencies of fat soluble vitamins might be associated with their use. It is probably advisable for other drugs to be taken at least one hour before, or four hours after doses of cholestyramine or colestipol.

Probucol

The most recently approved drug in the U.S for cholesterol lowering is probucol (4,4 -(isopropylidenedithio)bis(2,6-di-t butylphenol). In 1970 Barnhart and colleagues[illegible] reported that this sulphur-containing bis-phenol lowered cholesterol in normal mice, rats, dogs, and monkeys. The only toxicity noted in long term animal studies was an apparently species-specific sensitization of the dog myocardium to epinephrine, with consequent ventricular fibrillation.[illegible] Drake and associates[illegible] and Colmore and co-workers[illegible] confirmed the cholesterol-lowering action, observed satisfactory tolerance in human volunteers, and established an optimal daily dose of 750 mg. to 1 g.

Barnhart, Rytter and Molello[illegible] demonstrated cholesterol-lowering action in mice at dietary levels as low as 0075 per cent, and after a single 100 mg./Kg. intravenous dose. Probucol given to mice in the diet at a concentration of 0.06 per cent for 3 days did not significantly inhibit the incorporation of intravenously administered ^{14}C acetate into liver lipids. These investigators observed a decrease in digitonin precipitable radioactivity appearing in the serum after administration of labeled mevalonate, which may indicate an effect on lipoprotein synthesis or transport. Observations both in animals[illegible] and early studies in man[illegible] searching for abnormal amounts of desmosterol and/or 7-dehydrocholesterol were negative, indicating that probucol has no effect on the later stages of cholesterol biosynthesis. Other published studies do not establish with certainty the mode of action of this drug. Miettinen[illegible] reported in man an increase in fecal bile acids, especially during the period of cholesterol decrease, together with some diminution of synthesis. Kritchevsky and colleagues[illegible] found in rabbits fed 6 per cent corn oil and 2 per cent cholesterol, probucol at a diet level of 1 per cent, but not at 0.3 per cent, decreased the severity of atheromata in the arch and thoracic segments of the aorta.

Absorption of probucol from the gastrointestinal tract is limited and variable. Blood levels plateau after three or four months and decrease slowly on discontinuance (60 per cent in six weeks).[illegible]

During the administration of probucol over periods of 4 to 6 months to 14 diabetic and non-diabetic patients, Danowski and associates[illegible] observed an effect on cholesterol but no abnormalities in a battery of endocrine and metabolic indices, including hepatic function, tests of thyroid activity plasma cortisol, urinary steroids, blood glucose, serum insulin, and growth hormone response to oral carbohydrate. In a controlled clinical study which was conducted at the Clinical Research Institute in Montreal, the effect of diet and diet plus probucol was studied in a double-blind cross-over design. Probucol administration resulted in a mean reduction in total cholesterol of 12 per cent (and in low density lipoproteins of 15 per cent) in addition to that

Lorelco (The Dow Chemical Company).

produced by diet for a diet plus drug mean decrease of [illegible] per cent. No consistent effect was seen on triglycerides. Other clinical studies have confirmed a cholesterol lowering response with no consistent effect on serum triglyceride levels.[illegible]

It has been observed in several studies that the cholesterol decrease is unrelated to the pretreatment triglyceride level.

Taylor and associates [illegible] analyzing data on [illegible] subjects followed for a mean period of 3.6 years found gastrointestinal intolerance—mainly nausea and diarrhea—the only side effects apparently drug related, and this occurring with low incidence. In this open study with variable diet [illegible] per cent of the subjects showed a 10 per cent or greater decrease in cholesterol at 1[illegible] months; in [illegible] per cent the decrease was equal to or greater than 15 per cent. The mean decrease in 2[illegible] subjects remaining in the study for 48 months (responders) was 21 per cent. As in other data, no significant decrease in serum triglyceride levels was observed.

Discussion

For the rational use of the drugs discussed above it is critical that laboratory measurements be of maximally obtainable reliability and such that repeated tests are economically feasible. A cholesterol, 14 hour fasting triglyceride and examination of the gross appearance of a specimen after overnight in the refrigerator are sufficient in most instances.

Due [illegible] differences in methods and equipment considerable interlaboratory variability exists in cholesterol measurement. Values erroneously high by 20 mg/dl [illegible] more are not uncommonly reported. With [illegible] specific and reproducible enzymat[illegible] [illegible] into general use both precision and [illegible] variability should decrease. In the [illegible] should be sure that [illegible] sequential measurements, be [illegible] comparin[illegible] [illegible] preferably in the same laborat[illegible] [illegible]

Some judgm[illegible] [illegible] regarding what level of serum cholesterol [illegible] Many

A rough approximation [illegible] cholesterol can be obtained if triglyceride [illegible] ratio of triglyceride to cholesterol [illegible] HDL cholesterol of [illegible] in accordance [illegible]

LDL cholesterol $= TC - \frac{TG}{5} - 50$

laboratory charts persist in showing normal values up to or exceeding 300 mg./dl. Wright, [illegible] in a recent discussion of this subject, made a plea for considering the possibility that the optimal level for retardation of atherosclerosis may be under 200 mg./100 ml. He suggested that report sheets indicate the range of appropriate optimal values as 1[illegible]0 to [illegible]40 mg./dl. Much confusion would be avoided if the phrase *range of values for reference population* rather than *normal range* were used on such forms.

In regard to blood lipid abnormalities, there has been a continuing effort stimulated by the pioneering work of Gofman and associates [illegible] aimed to characterize circulating lipoproteins in a manner that gives a better correlation than total cholesterol with atheromatous changes of arteries, and thus clarify the relationship between lipemia and artery wall changes. Progress in this regard has been hampered by the time-consuming and expensive nature of methods using the ultracentrifuge and by the many difficulties inherent in meaningful quantitation of human arterial disease. Some of the possible links between hyperlipemia, platelets, and atheroma are becoming clearer.

Khachadurian and Kawahara[illegible] and Goldstein and Brown [illegible] have reported studies suggesting the presence of low density lipoprotein receptors on the surfaces of fibroblasts and other cells. Patients with familial hypercholesterolemia were shown to have a complete or partial deficiency of these receptors. The hypothesis was suggested that in normal cells the binding of low density lipoproteins to receptor sites facilitates degradation of LDL and also results in suppression of synthesis of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate controlling enzyme in cholesterol biosynthesis. Such a deficiency, by preventing cell ingress of cholesterol, eliminating the orderly feedback suppression of synthesis, could result in a high cholesterol level in the plasma and in interstitial fluid.

Dating back to the work of Choi and associates [illegible] there have been observations that serum high in cholesterol had a damaging effect on tissue culture cells. The effects of various lipoprotein fractions on activity of cells in culture is a subject of great interest in current research.[illegible] Ross and Glomset [illegible] have stated that the data available would suggest that a platelet factor is required to trigger cell proliferation, and that

other molecules such as the low density lipoproteins, have a supportive role.[13]

Twenty five years ago Barr, Russ, and Eder[4] observed that healthy men had higher levels of alpha lipoprotein than did men with coronary heart disease. Recently attention has been refocused on the alpha lipoprotein fraction, now usually referred to as high density lipoprotein. In several studies HDL appears to have a strong negative correlation with coronary heart disease and it is speculated that this fraction plays a scavenger role in returning excess cholesterol from the peripheral tissues back to the liver.[14] In some laboratories, both HDL and LDL are being divided into sub-fractions. It is hoped that early progress will be made in developing inexpensive methods to quantitate both LDL and HDL, together with their most meaningful components if such sub-fractionation appears desirable. These measurements are needed to better identify high risk patients and to better define the changes being produced by diet, drugs, exercise and alcohol.

Although this discussion has been largely limited to the role of total cholesterol and LDL in atherosclerosis, it should be noted that elevation of fasting triglyceride-rich very low density lipoproteins have also been implicated as a risk factor in atherosclerosis.[15] Whether this lipoprotein acts directly as a contributor to the lesion or acts by elevating LDL, is not known. Current theory holds that VLDL is the major precursor of circulating LDL so that its increased production and/or increased rate of degradation could be a mechanism for LDL increase. It has been speculated also that hypertriglyceridemia could contribute to cardiovascular events by accelerating the thrombosis mechanism or inhibiting thrombolysis.[16] It is advisable to evaluate fasting triglyceride levels prior to drug therapy of hypercholesterolemia and to monitor the level of this lipid periodically during management.

Conclusions

Although there still exist many controversial issues in regard to the cholesterol theory of atherosclerosis, the data that cholesterol-rich circulating low density lipoproteins are an important contributor to the progression of atherosclerosis are impressive.

The degree of uncertainty in this area of therapeutics, on critical reflection, is not really much greater than in many other areas of drug use. For the high risk patient there are currently available a variety of agents approved for lowering cholesterol which are reasonably effective and safe for long term use.

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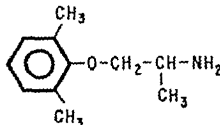
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Mexiletine

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Mexiletine (Boehringer Inglehem) (Fig. 1) is a new antiarrhythmic drug which is effective when administered orally or intravenously and is available in the United States for clinical investigation. Mexiletine is chemically similar to lidocaine and to tocainide, another new antiarrhythmic agent. It has been found effective in the treatment of acute and chronic ventricular arrhythmias associated with diverse cardiac diseases. Mexiletine has been the subject of a recent symposium and the current literature has been reviewed by Zipes and Troup



MEXILETINE

Fig. 1 1-(2',6'-dimethylphenoxy)-2-aminopropane (Ko 1173).

1 Clinical use

Mexiletine has been used in the treatment of ventricular arrhythmias associated with diverse cardiac diseases. Campbell and associates[1] used mexiletine on 91 occasions in 89 patients with ventricular premature depolarizations (VPDs) Mexiletine was administered intravenously as a 200 mg. bolus followed by an infusion of 3 mg./minute for 15 minutes after which a 100 mg. bolus was administered and infusion was maintained. Fifty five patients responded to mexiletine with a reduction in the frequency of VPDs $\geq$ 50 per cent, in 93 per cent of these patients, the reduction was > 75 per cent. Nine patients did not respond to mexiletine and in 27 the response could not be adequately determined. Four other patients with ventricular tachycardia (VT) received a single 200 mg. bolus injection of mexiletine. Two reverted to sinus rhythm and in two the rate of VT was reduced. The oral effectiveness of mexiletine was evaluated in 57 patients who received a total dose of 800 to 1,200 mg. over a 6 hour interval. Thirty-eight responded favorably to mexiletine Mexiletine also induced a favorable antiarrhythmic response in 24 of 35 patients with ventricular arrhythmias following myocardial infarction (MI) Lidocaine administered prior to treatment with mexiletine was without effect in these patients.

Fifty nine patients with ventricular arrhythmias resulting from MI, cardiac surgery or digitalis intoxication, received mexiletine intravenously as a 100 mg. bolus, or orally 600 mg. A total of 43 patients received intravenous mexiletine. A successful response to intravenous mexiletine was observed in 31 patients, partial success was seen in nine, and only three failed to respond. Sixteen patients received mexiletine by the oral route. Successful therapy was noted in 12, partial success in three, and failure in one. A successful response was one in which the arrhythmia was terminated or VPDs were reduced by 95 per cent. Partial success was a 75 per cent reduction in the number of VPDs or prolongation of the R R interval, so that the R-on T phenomenon did not occur

Talbot and colleagues[2] also studied the effects of mexiletine in patients who had MI cardiac surgery ischemic heart disease, or digitalis intoxication. Mexiletine was administered intravenously as a 150 to 200 mg. dose administered over

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10 minutes followed by 250 mg infused over 30 minutes, 250 mg./2.5 hours and 500 mg. over 8 hours. The oral dose of mexiletine was a 400 to 600 mg. loading dose followed by 600 to 1,200 mg./day For acute arrhythmias, 75 to 300 mg./Kg. was administered over 5 to 15 minutes followed by 1.5 to 3.0 gms. over a 36 to 48 hour period. Mexiletine was administered intravenously to 43 patients, 31 of whom responded successfully Partial control was observed in three. Oral administration of mexiletine resulted in suppression of non acute arrhythmias in 12 of 16 patients, partial suppression was obtained in three. Criteria for successful and partially successful treatment were the same as those mentioned in the preceding study

The efficacy of orally administered mexiletine has been studied in chronic treatment of ventricular arrhythmias associated with acute MI or ischemic disease or no apparent cardiac disease. Twenty four patients participated in the study and had one or more of the following: multiform VPDs, VPDs with a coupling interval < 400 msec. or R-on T phenomenon, VT or VF Mexiletine was administered as a loading dose of 400 to 600 mg. followed in 4 to 6 hours by maintenance doses of 450 to 1,050 mg./day Therapy was continued for a total of 11 4 patient years (range 1 to 16 months) Success of therapy was deemed complete if arrhythmias were totally abolished and partial if VPDs were decreased by more than 75 per cent with abolition of VT Using these *criteria, complete success occurred in 19 patients,* partial success in four and failure in one.

Studies have also been performed comparing the efficacy of mexiletine to other antiarrhythmic agents. The effects of mexiletine, procainamide and the β-blocker tolamolol were compared in patients with ventricular arrhythmias associated with a variety of cardiac disorders. Each patient was studied during four successive 2-week periods so that each received placebo mexiletine (600 mg./day) procainamide (4.5 mg./day) or tolamolol (300 mg./day) Antiarrhythmic effects were considered satisfactory if there was (1) complete abolition of all arrhythmias, (2) reduction by > 75 per cent of unifocal VPDs or reduction by 96 per cent of closely coupled VPDs or a reduction in the rate of VT Mexiletine, procainamide and tolamolol were approximately equivalent in ability to abolish VPDs totally Total suppression of coupled VPDs and VT occurred in approximately the same number of patients for mexiletine and procainamide tolamolol was somewhat less effective. Partial suppression of unifocal VPDs, coupled VPDs, and VT occurred to approximately the same extent for mexiletine and procainamide, whereas partial suppression after tolamolol was observed less often

Campbell and co-workers in a controlled, double-blind study of effects of mexiletine and procainamide on ventricular arrhythmias occurring after acute MI found that both drugs were equivalent in antiarrhythmic efficacy Sixty patients, treated previously with lidocaine were divided into three groups. One group received a placebo one received mexiletine, 250 mg. every 8 hours, and the third received procainamide 500 mg. every 4 hours. Seventy-seven per cent of patients receiving placebo showed serious ventricular arrhythmias compared with 33 per cent for those receiving antiarrhythmic drugs.

Other investigators have reported effects of oral and intravenous mexiletine on ventricular arrhythmias similar to those described above.

Effects on experimental arrhythmias. Mexiletine is effective against arrhythmias produced in experimental animals by ouabain, epinephrine or coronary artery ligation. Singh and Vaughan Williams infused ouabain to produced ventricular fibrillation in urethane-anesthetized guinea pigs. Mexiletine (3.3 mg./Kg., average dose) caused a reversion to sinus rhythm and increased *the dose of ouabain required to induce a* lethal arrhythmia. Pretreatment of guinea pigs with mexiletine 3 to 12 mg./Kg., however did not increase the dose of ouabain necessary to induce cardiac arrest. A similar study in dogs showed that mexiletine (average dose, 1.3 mg./Kg. intravenously) caused a reversion to sinus rhythm in eight of nine ouabain toxic dogs studied Also, in this study it was shown that VPDs induced in halothane-anesthetized dogs by injection of epinephrine, 3.2 μg/Kg. were completely abolished by mexiletine, 0.25 mg./Kg. intravenously

Arrhythmias occurring after ligation of the left anterior descending coronary artery in dogs are reduced by mexiletine 2 to 8 mg./Kg., intravenously[13] with almost complete suppression of ectopic pacemakers at the highest doses. This effect of mexiletine persisted for at least 30 minutes after injection. The frequency of beats originating from the sinus node increased from

approximately 17 per minute during control to a maximum of 123 at 5 minutes following mexiletine, 8 mg./Kg. while the total ventricular rate which included beats originating from the sinus node as well as from ventricular ectopic pacemaker sites decreased from 164 to 139.

Mexiletine also prevents the decrease in threshold current required to initiate repetitive ventricular beats in pentobarbital-anesthetized dogs following ligation of the left anterior descending coronary artery.

2. Pharmacokinetics

Mexiletine is almost completely absorbed following oral administration. Prescott and associates[15] found that, in healthy individuals peak plasma levels are reached within 2 to 4 hours after mexiletine, 3 mg./Kg. (in water) or 400 mg. capsules. However in patients with myocardial infarction who have had narcotic analgesics, peak plasma levels were not reached until 4 to 6 hours. The authors suggest that any agent (e.g., atropine) which may inhibit gastric emptying would delay attainment of peak plasma levels.

The average half life of elimination ($t_{½}$) of mexiletine in healthy individuals is approximately 10 hours after an oral dose whereas in patients with MI, $t_{½}$ ranged from 7.8 to 25.3 and 6.7 to 18.5 hours for intravenous and oral administration, respectively.[13] This difference in $t_{½}$ for healthy and diseased individuals may reflect a decrease in hepatic blood flow in patients with MI.

One of the major advantages of mexiletine is its efficacy when administered orally. In contrast to lidocaine which has a *systemic availability* of about 30 per cent after an oral dose, the value for mexiletine is approximately 88 per cent. The apparent volume of distribution for mexiletine has been reported to be large (approximately 500 liters/Kg.).

Following rapid intravenous injection, plasma mexiletine concentrations decreased rapidly and the distribution of mexiletine has been explained using a three-compartment model.[13] These investigators suggest that the first compartment consists of the blood and highly perfused tissues including heart, brain, liver, kidney, and lung. The second and third compartments consist of deep or peripheral tissues such as muscle, fat, and skin.

Mexiletine is reported to be approximately 70 per cent protein bound and the concentration in whole blood is reported to be nearly 15 per cent higher than in plasma.

Mexiletine is eliminated from the body through metabolism (probably hepatic) and only 7 to 8 per cent of a dose of mexiletine was recovered unchanged in the urine of healthy individuals over a 3-day period.[13] Although little of a given dose of mexiletine is eliminated by the renal route, this process is pH-dependent so that at a lower urinary pH, more mexiletine would be cleared renally.[14]

3. Clinical toxicity

In light of the similarities in chemical structure of mexiletine and lidocaine, it is not unreasonable for side effects of each to be similar. As with lidocaine the most frequently reported side effects of mexiletine are manifested in the central nervous system (CNS) and include tremors, nystagmus, blurred vision, dizziness, drowsiness, confusional state, mild ataxia, paresthesia, dysarthria, insomnia, and tinnitus. Other side effects may be exerted on the gastrointestinal tract including dyspepsia, nausea, vomiting, and anorexia. Other less commonly occurring signs include cardiovascular toxicity: a broadening of the QRS complex, complete atrioventricular dissociation, hypotension with bradycardia and sinus arrest, sinus tachycardia, atrial fibrillation (with a variable ventricular response) postural hypotension, and dyspnea.

Therapeutic plasma levels have been reported to range between 0.5 to 2.0 µg/Kg. Mild signs of mexiletine toxicity may occur more frequently at the upper limits of this range and more severe signs of toxicity have been reported to occur between 1.5 to 3.0 µg/ml. Despite reports of mexiletine toxicity in one study concentrations of mexiletine which exerted an antiarrhythmic effect caused significant side effects in four of 25 patients studied while procainamide, at therapeutically effective levels, caused side effects in 12 of 25 patients.

4. Hemodynamic and autonomic effects of mexiletine

Mexiletine has few effects on hemodynamic parameters. Pozenel[16] studied the effects of mexiletine in patients with atrial and/or ventricular arrhythmias. Mexiletine (50 to 100 mg. intravenous injection or 350 to 500 mg. infusion) has no significant effect on arterial blood pressure (sys-

tolic, diastolic or mean) left ventricular stroke work, heart rate, pulmonary arterial pressure (mean or end-diastolic) cardiac index or total peripheral resistance. Similarly Kuhn and co-workers, in a study of patients with ventricular arrhythmias, found that oral mexiletine 600 mg. caused no statistically significant change in cardiac output, pulmonary arterial pressure (systolic or diastolic) or systemic arterial blood pressure, although there was a tendency for values for these parameters to decrease slightly

Banim and colleagues determined effects of a single intravenous dose of mexiletine, 1.5 mg./Kg on hemodynamic parameters at rest, during atrial pacing, and during mild exercise At rest, small but statistically significant changes were seen Heart rate decreased by 4 beats/minute, and increases were noted in pulmonary arterial systolic pressure (3 mm. Hg) left ventricular end-diastolic pressure (1.3 mm. Hg) and left ventricular systolic pressure (4.2 mm. Hg) During atrial pacing at a rate of 100 beats/minute, no effect of mexiletine was observed on any of the above parameters or on cardiac output, stroke volume, and LV dp/dt. During mild exercise, cardiac output decreased by 0.5/minute and LV dp/dt decreased (101 mm. Hg)

Mexiletine exerts little effect on contractility of isolated cardiac preparations. Isometric and isotonic contractile force is decreased slightly at concentrations of mexiletine ≤ 10 mg./L. At mexiletine concentrations of approximately 80 to 90 mg./L., contractile force is decreased appreciably Studies of experimental animals suggest that mexiletine has little effect on the autonomic nervous system. In guinea pigs, atropine had no effect on the bradycardia induced by mexiletine 3 mg./Kg. intravenously Vagally induced bradycardia in cats was similarly unaffected by mexiletine. Similarly it has been reported that the effects of mexiletine are not mediated by the sympathetic nervous system.

5 Effects on cardiac impulse initiation and conduction

Therapeutic plasma concentrations of mexiletine exert little effect on cardiac impulse initiation and conduction Roos and co-workers studied the effects of mexiletine in 25 patients at the time of cardiac catheterization. Thirteen had apparent conduction defects and five showed apparently normal conduction. Mexiletine 200 to 250 mg., was administered over a 5 minute interval and was followed by a continuous infusion of 60 to 90 mg./hr Mean plasma levels of mexiletine ranged from 0.83 to 1.65 µg/Kg., except for two patients in whom toxic levels of mexiletine were attained (i.e., ≥ 3 µg/ml.) Mexiletine exerted no significant effect on sinus rate atrial refractoriness, or sinus node recovery time. A H intervals showed a slight but non significant decrease and A V nodal refractoriness was not consistently changed. H V intervals were increased slightly but non significantly The effective refractory period of the His-Purkinje system, determined in five patients, showed a mean increase of 127 msec. In four of these five patients, however infra His conduction disturbances were known to exist prior to administration of mexiletine. In two patients with pre-existing complete heart block, mexiletine had no effect on the frequency of the junctional escape rhythm in one and in the other was associated with a period of cardiac arrest (lasting for 14 seconds) after administration of mexiletine.

In another study[30] 20 patients having coronary artery disease, (all in sinus rhythm) received mexiletine 3 mg./Kg. intravenously over a 10 minute interval. Mexiletine had no effect on sinus rate or sinus node recovery time. Similarly atrial effective and functional refractory periods were unchanged. A H and H V intervals were not affected by mexiletine. A V nodal refractory periods were not significantly affected by mexiletine nor was right ventricular refractoriness. The relative refractory period of the His-Purkinje system, however was decreased from 422 to 379 msec. This change was statistically significant and was associated with a broadening of the QRS complex in eight of nine patients.

Effects of mexiletine on isolated cardiac tissues have been studied using a variety of experimental models. Singh and Vaughan Williams found that mexiletine, 5 µg/ml., had little effect on spontaneous rate of isolated rabbit atria. Conduction velocity and the maximum rate at which the tissue could be stimulated were decreased by mexiletine, 3 to 5 µg/ml. Studies using microelectrode techniques have shown that mexiletine decreases the maximum rate of phase 0 depolarization (V_{max}) of rabbit atrial and ventricular muscle[11] and ungulate Purkinje fibers.[11] Membrane responsiveness of Purkinje fibers is decreased. Similarly in these tissues, action

potential duration is decreased by mexiletine,[21, 22] apparently more so at the region of maximum duration than at more proximal or distal sites,[22] so that action potential duration becomes more uniform throughout the ventricular specialized conducting system. The effective refractory period of canine Purkinje fibers is similarly decreased by mexiletine (≤ 5 μg/mL) and conduction velocity in this tissue is decreased by mexiletine.[22]

In one study automaticity of ungulate Purkinje fibers (arising as a result of superfusion with a solution containing $[K^+]_o = 2.2$ mM or isoproterenol) was decreased by mexiletine, 1 to 10 μg/mL, apparently by a shift in threshold voltage to a more positive level. Phase 4 depolarization was not significantly altered by mexiletine at concentrations which suppressed the rate of spontaneous action potential initiation. An effect of mexiletine, however on phase 4 depolarization of canine Purkinje fibers has been reported.[22] Concentrations of mexiletine of 2 to 22 μg/mL decreased the slope of phase 4 depolarization with a concomitant decrease in spontaneous rate. The reason for the reported difference between mexiletine effects on phase 4 depolarization may be species variability. Further investigation will help clarify this effect of mexiletine and aid in determining which of these cellular electrophysiologic effects of mexiletine may be responsible for its antiarrhythmic action.

Conclusions

Mexiletine is a useful antiarrhythmic agent effective against ventricular arrhythmias associated with a variety of cardiac diseases. Its oral effectiveness and its relatively low incidence of serious side effects indicates that mexiletine should take its place among clinically effective antiarrhythmic drugs.

The author wishes to express his gratitude to Dr. Michael R. Rosen for his editorial assistance and to Mrs. Cynthia Brandt for her secretarial assistance.

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Annotations

Hematocrit, viscosity and cerebral blood flow

The relationship between elevated hematocrit (Hct) and brain disease has been of interest for some time. There is an increased incidence of strokes and transient ischemic attacks (T.I.A.) in patients with polycythemia vera, although platelet function abnormalities may play a critical role in this disorder. The concept that [illegible] pure erythrocytosis may be significant in a variety of disease states has recently received much attention. For example, it has been reported that Hct elevations may be related to intermittent claudication and ischemic heart disease. In addition, it has been claimed that there is [illegible] fold elevation in mortality rate in patients with pseudopolycythemia (Gaisböck syndrome). More recently a group from the Institute of Neurology, Queen Square, London, have reported [illegible] significant reduction in cerebral blood flow (CBF) in patients with Hct values in the upper range of normal (47 per cent to 53 per cent). They subsequently found the CBF increased by a mean of [illegible] per cent in these patients following repeated venesection, along with [illegible] decrease in the incidence of T.I.A.s. A significant reduction in whole blood viscosity was felt to be responsible for these findings.

Although the hypothesis that reduced Hct → reduction in blood viscosity → increase in CBF → improvement in symptoms is an attractive one, there are theoretical considerations which render it suspect. For example, the viscosity of whole [illegible] is influenced by many [illegible] factors aside from Hct. Also of [illegible] are the flexibility of red blood cells, aggregation of cellular elements, rate of blood flow [illegible] vessel bore, and plasma protein and fibrinogen concentrations. In addition, it has been shown that the shear rate dependency of viscosity [illegible] directly with the Hct. Since the Hct in the microcirculation has been found to be less than the [illegible] venous Hct, and since viscosity plays [illegible] lesser role in smaller vessels, blood viscosity in the microcirculation may have [illegible] negligible effect on flow rates. This may be of particular importance in the cerebral circulation, where the vessels determining flow are of small diameter. Also, the main factors in determining flow in the microcirculation appear to be the deformability of red blood cells and the occurrence of emboli or cellular aggregates, and not viscosity. From an experimental point of view it has been found that viscosity elevations up to five times normal [illegible] little effect on CBF in dogs with [illegible] CBF changes explained by alterations in O carrying capacity. Finally, it is felt by many investigators that [illegible] significant changes in blood viscosity [illegible] occur [illegible] Hct values of 0.55[illegible]

Epidemiological evidence has also been [illegible] relating to the Hct–cerebrovascular disease relationship. Data from the Framingham study[illegible] revealed [illegible] correlation between Hct (within the normal range) and [illegible] cerebral infarction. However, when hypertension was taken into account, the residual risk associated with elevated Hct was not significant. Studies of hemoglobin and ischemic heart disease revealed a similar correlation, but these also were not significant when the data were adjusted for hypertension. A small but significant negative correlation has recently been observed between cerebrovascular disease mortality rate and increasing altitude in the United States. Although other factors may be involved, the finding of lower stroke mortality at higher altitudes (with correspondingly higher Hcts) is not consistent with the proposed Hct–viscosity–cerebrovascular disease relationship. To date there is no evidence linking elevated Hct within the normal range with coronary artery or cerebrovascular disease on an independent basis.

While the CBF experiment reported by the British group may not be related to viscosity as suggested, it is an intriguing finding. The most essential question is the effect of Hct changes on flow in diseased vessels. It is likely that the normal flows maintained with elevated viscosity reported in animal experiments are due to metabolic control mechanisms intrinsic to the cerebral circulation. It is possible that in patients with pre-existing cerebrovascular disease, the relatively small viscosity changes associated with high Hct produce CBF alterations because of defective autoregulation. However, the finding of lower CBF with Hct from 4[illegible] per cent to [illegible] per cent is surprising and certainly would not be expected from analysis of the factors discussed above. Further studies of the Hct–CBF relationship would be expected to settle this important issue. This could easily be done utilizing CBF data already collected.

The clinical question of phlebotomy (recommended by Thomas and colleagues[illegible] for patients at risk for ischemic vascular disease with Hct [illegible] consistently above [illegible] per cent) [illegible] of potentially great importance. There have already been suggestions both on empirical and experimental grounds for judicious phlebotomy in patients at risk for coronary artery disease with high Hct [illegible] in the normal range.[illegible] While definitive evidence supporting venesection in such patients is presently lacking, carefully controlled double-blind prospective studies designed to answer these questions are clearly indicated.

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Nonbacterial thrombotic endocarditis and myocardial infarction

Nonbacterial thrombotic endocarditis (NBTE), an entity characterized by bland fibrin-platelet thrombus on cardiac valves and the absence of microorganisms or valve destruction, may be the cause of significant morbidity and mortality as a result of major arterial embolization. NBTE is no longer regarded as a pathologic curiosity, occurring in about 1.6 per cent of adult deaths. It is associated with a variety of diseases, most commonly malignant tumors. Adenocarcinomas, particularly mucin-secreting types, predominate in most series. The pathogenesis of NBTE is not clear; disseminated intravascular coagulation and thrombotic phenomena are not infrequently encountered, suggesting a pathogenetic role of coagulation abnormalities (hypercoagulable state) in some cases.

Coronary embolism with myocardial infarction is one of the dreaded complications and was found in 6.7 per cent and 9 per cent of patients with NBTE in two recent studies. Thromboembolism, usually of the intramyocardial arteries, without myocardial infarction, is found more frequently but is not judged to be of clinical significance. All patients described so far have had underlying malignant neoplasms, characteristically of epithelial origin. This complication of NBTE has been reported in patients of both sexes with ages ranging from the third to the eighth decade.

Pathologically, the vegetations of NBTE are small, measuring less than 10 mm, and usually situated on the closure or free margins of the valves. As may be expected, most structures are located on the mitral and aortic valves. The pathologic alterations in the hearts of patients with myocardial infarction associated with NBTE are not distinctive. The heart may be normal or moderately enlarged. An underlying cardiac disease such as rheumatic valvulitis may be present. The intramyocardial or coronary arteries or both frequently contain thromboemboli. Histologically, multiple acute infarcts of different ages are usual. A single area of infarction may result when the embolus lodges in a coronary artery or large intramyocardial artery. This was described in three of six cases published recently. The pathologic diagnosis should be accepted only in the presence of embolic occlusion of coronary arteries or their branches and in the absence of significant atherosclerosis or other diseases of coronary arteries.

The antemortem diagnosis of NBTE-associated myocardial infarction is difficult but not impossible. Most patients have concomitant neurologic symptoms probably secondary to cerebral embolism. These symptoms may mask the chest pain that would alert physicians to the diagnosis of myocardial infarction. Severe symptoms and signs resulting from embolization to other organs—kidneys, spleen, the gastrointestinal tract—may further complicate the clinical picture. The diagnosis under these conditions would depend on a high index of suspicion. It is suggested that, in the patient at risk (with carcinomatosis or other disseminated malignant neoplasms), there should be intermittent monitoring with noninvasive techniques such as electrocardiograms, cardiac enzyme studies and screening for evidence of disseminated intravascular coagulation, venous thrombosis or hypercoagulable state by determining platelet counts, partial thromboplastin time, prothrombin time, and levels of blood fibrinogen and fibrin split products. The latter in combination with nonspecific signs such as changing murmurs and purpuric skin lesions may indicate the presence of NBTE, thus increasing the potential for the diagnosis of myocardial infarction. In most patients, the clinical status and the severity of the underlying disease would preclude coronary angiography; coronary

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embolectomy or bypass graft. Conservative management is therefore advised.

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Absence of any change in thyroid function following acute myocardial infarction

Since thyroid hormones specifically stimulate one of the adenyl cyclase systems in myocardium, any change in thyroid function, which occurs after acute myocardial infarction would be of potential clinical significance. Previous observations in this regard have produced conflicting findings. The object of the present study was to determine the effect of acute myocardial infarction on the function of the hypothalamic-pituitary-thyroid axis.

Ten patients admitted to hospital with acute myocardial infarction were studied. The diagnosis was confirmed by ECG and enzyme changes and informed consent was obtained in each case. Total thyroxine (TT), free thyroxine (FT), total triiodothyronine (TT), free triiodothyronine (FT) and thyroid stimulating hormone (TSH) were measured and thyrotrophin releasing hormone (TRH) test was performed 4 hours after the acute incident. These tests were repeated 14 days later.

Total thyroxine, TT and TSH were measured by radioimmunoassay by the methods of Challand and associates and Hall and colleagues. Free thyroxine and FT were derived from the TT and TT and the dialysable fractions obtained by equilibrium dialysis. All data were subjected to Student t test for paired data.

The results obtained are shown in Table I. All results for individual patients were within the normal ranges and there were no significant differences between any of the baseline parameters nor in the TSH response to TRH at 4 hours and 14 days after acute myocardial infarction.

It has been suggested by Wahner and others that previous investigators were unable to demonstrate changes in thyroid function in patients with myocardial infarction because of inadequate diagnostic criteria. In the present study the same criteria as theirs were used but nevertheless has failed to demonstrate any change in thyroid function, thyroid hormone binding, or in the hypothalamic-pituitary-thyroid axis after acute myocardial infarction.

It is possible that these discrepancies are due to differences in the severity of the patient's illness rather than in the diagnostic criteria used.

Table I

	Time after acute myocardial infarction	
	4 hours (mean ± SD)	14 days (mean ± SD)
TT (nmol./L.)	8 ± 14	81 ± 11
TT (nmol./L.)	1.6 ± 0.4	1.8 ± 0.4
FT (pmol./L.)	20 ± 6.0	22 ± 7.0
FT (pmol./L.)	3.3 ± 1.6	3.4 ± 1.0
TSH—basal—(mu/L.)	3.5 ± 1.2	2.1 ± 1.6
TSH—20 minutes after TRH—(mu/L.)	11.5 ± 4.5	9.6 ± 2.5

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Of jogging

A popular fad today is jogging—exercising to death or health, who knows? It is a dangerous fad. The American Automobile Association reports that 8,200 joggers in the U.S.A. have been killed by automobiles and over 100,000 injured during 1977. Most joggers jog because they believe the exercise will help keep them physically fit and healthy for a long life. But, has it been shown that jogging or any organized exercise is good for the heart? That such exercise is beneficial would be almost impossible to establish beyond scientific doubt. There are many variables involved. But, it can be shown that jogging is injurious to many people beyond any doubt. When automobiles kill or injure thousands of joggers, then jogging becomes a serious and dangerous disease of the environment, industry and transportation. This certainly becomes evident when a young jogger dies while jogging, or develops a myocardial infarction or an episode of angina pectoris or any other type of injury such as to the feet, knees, back, etc. Therefore, upon what logical basis is jogging recommended as therapy or as a health practice? Why should one jog? Why one should *not* jog can be supported by much positive data.

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Letters to the Editor

Nitrates, pharmacological phlebotomy and pulmonary edema

To the Editor:

The paper by Drs. Strauer and Scherpe[1] demonstrates by a very elegant method the existence of a pharmacological phlebotomy after the use of nitrates. We have been particularly interested to note that the reduction in blood volume they observed (437 ml.) was very close to the figures we found in 1972 for the reduction in central blood volume (385 ml.) measured by radiocardiography with Indium 131 after the administration of 5 mg. of sublingual isosorbide dinitrate. Recently we confirmed this point by observing with intravenous nitroglycerin (45 mcg./minute) a reduction of 300 ml. by the dye dilution curve methods. In our work total circulating blood volume measured by Chromium 51 did not decrease after isosorbide dinitrate.

Although none of the methods used can define properly the precise anatomic significance of the measured volume, we believe that the method is adequate to study modifications in the same patient induced by drugs. Strauer and Scherpe, as well as ourselves, do demonstrate by these studies a decrease in central blood volume and bring further light on the mechanism of action of nitrates in the treatment of pulmonary congestion and edema. We have observed both by sublingual isosorbide dinitrate and by intravenous nitroglycerin a fairly constant and sometimes spectacular improvement in clinical and hemodynamic parameters associated with that condition and in refractory pulmonary edema.

We believe that the reduction in central blood volume following the increase in venous capacitance is the main event responsible for the decrease in filling pressures. We believe that oral nitrates used at adequate doses can be profitably used not only in the initial treatment of acute pulmonary edema in emergencies but also in the management of chronic heart failure to reduce pulmonary transudation and eventual acute episodes of pulmonary hypertension. We think that the maintenance under continuous nitrate therapy associated with digitalo-diuretic drugs, resulting in some decrease of the central blood volume and of pulmonary pressure facilitates ventricular performance and reduces chronic transudation, which is usual either at rest or during exercise in the course of chronic left ventricular failure.

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Systemic vascular pooling potency of vasodilator drugs (nitroglycerin, phentolamine, hydralazine)

To the Editor:

In his Letter to the Editor Dr. Paul Chiche refers to results concerning the systemic vascular pooling effects of nitroglycerin in man. In these studies a defined dosage of nitroglycerin was used (mean 40 mcg./minute) in order to produce a reduction in central blood volume by 300 and 385 ml. (mean), respectively. These figures, though somewhat lower than in our study[1] (mean dosage of nitroglycerin, 62 mcg./minute intravenously, mean reduction in central blood volume 437 ml.) are in excellent agreement with our results. Thus, the effectiveness of intravenous nitroglycerin in producing an internal, i.e., pharmacological phlebotomy is demonstrated. It may be reasonable to assume that the beneficial effects of nitroglycerin in acute pulmonary congestion may be due to this acute reduction in central blood volume.

It is obvious that the effectiveness of vasodilator to ameliorate acute pulmonary congestion runs in parallel with its venous pooling potency. A primary action of vasodilating drugs is to relax vascular smooth muscle. Thus, alterations (a) in venous capacitance and pooling, (b) in arteriolar and arterial dilatation, or (c) in resistance and flow changes of both sides of the circulation may occur. For clinical and therapeutical reasons a vasodilating drug will be of high

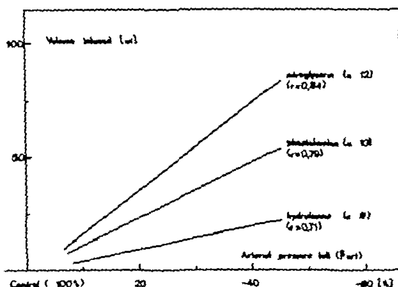


Fig. 1 Relationship between arterial pressure fall (per cent, on the abscissa) and the volume expansion (in ml on the ordinate) necessary for restoration of arterial pressure following the intravenous administration of three vasodilating drugs (nitroglycerin, phentolamine, and hydralazine).

effectiveness in the treatment of pulmonary congestion if it preferably exerts its effects on the venous side of the circulation associated with effective, acute reduction in central blood volume, but without considerably lowering arterial blood pressure. This means that the ratio of central blood volume change per change in arterial blood pressure may be practical measure of the over-all and systemic vascular pooling potency of vasodilating drug.

In order to comparatively evaluate the systemic vascular pooling potency of three clinically used vasodilators (nitroglycerin, phentolamine, hydralazine), series of 31 closed-chest experiments in healthy cats was performed. The vasodilators were given in fractions appropriate to lower the mean arterial blood pressure in defined steps below the controls. Then, dextran (Macrodex, Knoll GFR) was intravenously infused until venous and arterial pressures had reached the initial values, that is the control values, before starting vasodilation. The amount of dextran necessary for the restoration of pressures was determined in all experiments.

Systemic vascular pooling potency was quite different for these three vasodilating drugs (Fig. 1). Regression lines between the per cent arterial pressure change (x) and the volume amount infused (y) necessary for blood pressure restoration are: Y = -1.78 + 1.88 X (r = 0.84, nitroglycerin), Y = 1.79 + 1.25 X (r = 0.79 phentolamine) and Y = -0.77 + 0.50 X (r = 0.71, hydralazine). For a given amount of arterial pressure fall (e.g. by 20 per cent from the initial controls) an infusion of 35 ml (mean) was necessary to restore arterial blood pressure under the influence of nitroglycerin, whereas 23 ml. (mean) were needed for phentolamine and only 9.4 ml (mean) for hydralazine. Similar relationships were present when considering central venous pressure. As indicated by the steepness of regression lines (Fig. 1), reduction in central blood volume to arterial pressure fall ratio of 1.88 (nitroglycerin), of 1.25 (phentolamine), and of 0.50 (hydralazine) was present.

From these findings it is obvious that the systemic vascular pooling potency decreases from nitroglycerin to phentolamine and is lowest under the influence of hydralazine. In a similar sequence the preload reducing potency of these drugs decreases, whereas the afterload reducing potency increases. Thus, nitroglycerin possesses preferably preload reducing effects, whereas hydralazine exerts preferably afterload reduction. Phentolamine seems to affect pre- and afterload similarly. For therapeutical interventions which primarily require preload reduction (e.g., in acute pulmonary congestion), nitroglycerin may be useful. In contrast, in diseases which primarily require afterload reduction (e.g., in acute hypertensive heart failure), hydralazine may be preferred. These estimates do not consider the possible effects on e.g. heart rate, cardiac output, and contractility which in turn may influence the clinical indication of these vasodilating drugs.

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Coronary artery spasm and mitral valve prolapse

To the Editor:

In the April, 1978, issue of AMERICAN HEART JOURNAL (Coronary artery spasm and mitral valve prolapse, AM. HEART J 95:457, 1978), Dr. Buda and associates concluded: "These data suggest an association between coronary artery spasm and mitral valve prolapse. Coronary artery spasm may thus be an important factor in the pathogenesis of the chest pain, arrhythmias, electrocardiographic abnormalities, and sudden death, that have already been described in some patients with mitral valve prolapse" (p. 462). Three major objections to the paper and its conclusion are apparent.

1. Figs. 3 and 6 in their article do not demonstrate mitral valve prolapse. The normal mitral valve is shown, without evidence of true prolapse into the left atrium. The authors' angiographic criteria for mitral valve prolapse is apparently based on references 11, 12, and 13 in their paper. References 11 and 12 do, in fact, show typical cases of mitral valve prolapse which in no way look similar to the ones published by Buda and colleagues. Reference 13 is a pathological study only. It does not include angiographic correlations. The mitral valve recess has been frequently mistaken for mitral valve prolapse; rigorous criteria appear necessary for its diagnosis.

2. Prinzmetal's angina is indeed related to spasm of the coronary arteries. The clinical syndrome of Prinzmetal's angina has a limited duration, is associated with chest pain occurring at rest and not on exercise, has dramatic electrocardiographic changes, may have malignant arrhythmias, and usually has a poor prognosis. The clinical syndrome of mitral valve prolapse is obviously very different.

3. Eight of the ten patients had catheter-induced spasm, a finding usually not associated with clinical manifestations of chest pain or electrocardiographic changes. Two other patients were reported to have spontaneous spasm, but neither showed chest pain or ECG changes during spasm.

In conclusion, the association between coronary artery spasm and mitral valve prolapse does not appear to be supported by the data presented by the authors.

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Reply

To the Editor:

We thank Drs. Pichard and Herman for their comments regarding our article. In response to their first point, we agree that rigorous criteria are necessary for the angiographic diagnosis of mitral valve prolapse. Our angiographic criteria for mitral valve prolapse are based on previous angiographic-morphologic correlates. Since mitral valve prolapse is a dynamic event, it can be best appreciated on cineangiographic study and may not be adequately illustrated on end-systolic frames, particularly if the plane of the mitral valve ring is not indicated. Both cases No. one and nine (Fig. 6 and 3) had definite angiographic prolapse of the posterior mitral leaflet beyond the plane of the mitral valve ring into the left atrium.

We agree with Drs. Pichard and Herman's second point. We did not imply that Prinzmetal's angina and mitral valve prolapse were clinically similar syndromes. In fact, only one of our patients with mitral valve prolapse (case No. one) had classical Prinzmetal's angina. However some patients with mitral valve prolapse do have typical anginal chest pain, dramatic ECG changes, myocardial infarction, malignant ventricular arrhythmias, or sudden death.[2-4] It is this particular subgroup of patients in whom underlying coronary artery spasm may be suspected.

With regard to Drs. Pichard and Herman's final point, the true significance of "catheter induced" spasm is yet unknown. Since a catheter factor cannot be excluded in any case where the coronary artery is cannulated, the categorization of coronary artery spasm into "spontaneous" or "catheter-induced" is somewhat arbitrary and relates usually to the location of spasm. It is of interest that in some of the earlier reports of patients with Prinzmetal's angina where coronary spasm was documented, it occurred in locations where it could be attributed to mechanical catheter irritation. The finding of proximal ("catheter-induced") spasm and distal ("spontaneous") spasm in the same patient is not unusual. It is yet unclear whether "catheter induced" spasm may occur only in patients with a predisposition to spasm. The occurrence of chest pain and ECG changes is most likely related to the severity rather than to the location of the spasm and the resulting decreased coronary perfusion. Other investigators have commented on the possible association of mitral valve prolapse and coronary artery spasm. Recently Sabom and colleagues[5] have elicited ergonovine-induced coronary artery spasm in some patients with mitral valve prolapse.

We feel our observations are valid in this preliminary study. Although, coronary artery spasm and mitral valve prolapse may be associated in some patients, the question as to whether this association is fortuitous or of pathogenic importance remains unresolved and speculative.

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PR segment depression, pericardial knock, and pericardial rub in pericarditis

To The Editor:

The paper by Wheatley[1] on acute pericarditis in calcific aortic stenosis is an interesting and well-presented discussion of the interaction of two pathologic conditions in the same patient. I should like, however, to add a few remarks to some of the data and the discussion.

Dr. Wheatley's Fig. 1 shows an electrocardiogram of left ventricular hypertrophy. With the T-P interval representing the appropriate baseline, there are, indeed, ST (J) elevations. These occur in only four leads, and there are as many ST depressions as elevations plus an equal number of isoelectric J-points. The ST elevations, notably in Leads V to V are of an order frequently seen with deep S waves and sometimes considered "reciprocal" to the ST depressions of LVH in the lateral precordial leads. What is more striking about this electrocardiogram is the PR segment depressions in Leads I, II, III, aV and V to V. These are equally characteristic of acute pericarditis as are ST elevations and, indeed, in this ECG are the principal sign of pericarditis.

Amid the interesting clinical information and its correlation with the operative and pathologic findings is the presence of "pericardial knock." An abnormal third heart sound of this kind would virtually never be found in pure cardiac tamponade, although it is characteristic of constriction, and can be heard and recorded in combined effusive-constrictive pericarditis. To some extent that combined lesion may have been present, since the pericardium was thickened and, on the photomicrograph (Fig. 4), the epicardium may actually be both thickened and neovascularized. If not, the patient's pericardial knock requires further discussion as possibly a strong third heart sound associated with the diminished ventricular compliance of LVH and not suppressed by tamponade.

Finally, the presence of the pericardial rub is also of interest and is consistent with the observation that pericardial rubs are the rule (rather than, as traditionally taught, the exception) in the presence of effusions which can be quite large, with or without tamponade.

These remarks are meant to supplement and not to detract from the nice presentation of an interesting subject.

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Reply

To The Editor:

I am very grateful to Dr. Spodick for his additions to my presentation. His enlargement of the electrocardiographic changes are particularly appropriate. The TP segment must be considered the baseline when acute pericarditis is suspected since it is the only segment which is isoelectric. This allows detection of PR and ST segment shifts. His references 2 and 3 are excellent discussions of this subject.

The sound designated as a "pericardial knock" was at the appropriate time interval after the second sound in early diastole and was either a knock or a third sound, but the frequency of this sound was higher than a third heart sound. Since the first and second sounds were greatly reduced at the apex and this sound was heard easily, it seemed unlikely to be a third sound. Surface recordings were not made.

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Misdiagnosis of pericardial effusion in presence of MAC

To The Editor:

Dashkoff and associates[1] in their article, "Echocardiographic features of mitral annulus calcification (MAC)," state that the echoes from the calcified annulus are contiguous with the echoes from the posterior aortic wall.

Their figures 5, 6, and 8 clearly demonstrate that it is the

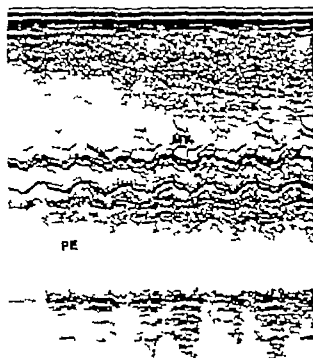


Fig 1 Echocardiogram from a patient with chronic renal failure on dialysis and with secondary hyperparathyroidism. The mitral valve annulus is calcified. Both mitral valve (*MV*) leaflets are clearly demonstrated. There is a large pericardial effusion (*PE*). The left ventricle is dilated (7 cm.) due to the surgical A V *shunt*

terior mitral leaflet which is contiguous with the posterior aortic wall and not the calcified annulus. The echoes from the annulus disappear when the posterior aortic wall is seen, they are more posterior and they *discontinue at the mitral–left* atrial junction.

The authors say that misdiagnosis of pericardial effusion can be made in the presence of MAC. We recently examined ten chronic dialysis patients with pericardial effusions and MAC. These patients tend to develop multiple metastatic calcifications due to malfunction of their parathyroid glands (secondary hyperparathyroidism). Fig 1 demonstrates such a patient with a large pericardial effusion and MAC. It is clear that the calcification is in the annulus since both mitral valve leaflets are demonstrated

Thus, with appropriate gain settings, one should not misinterpret MAC as pericardial effusion

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Reply

To the Editor

Dr Glaser's comment regarding anatomic discontinuity between the normal mitral annulus and the aortic root is correct. The normal mitral annulus is not a complete circle but is rather horseshoe in shape being absent at the root of the aorta. This explains why many patients with MAC have radiographic J or "U"-shaped calcific densities. However when MAC is very extensive, it commonly involves the aortic root including the aortic valves, and the extent of aortic valve calcification is qualitatively related to the severity of MAC. Under those circumstances, complete circular MAC may be seen roentgenographically and an echocardiographic scan of the left ventricular outflow tract will frequently demonstrate close approximation of thickened echoes emanating from the mitral annulus and the posterior aortic wall.

Moreover when the echoes recorded from a heavily calcified *annulus are extremely intense, excessive reduction in echocardiographic* gain is often required in order to achieve optimal display In so doing, over-attenuation of posterior left ventricular wall echoes can result in an echo-free space below the annular echoes, even in the absence of significant pericardial effusion. The annular echoes can be mistaken for the left ventricular wall and the left ventricular wall for pericardial effusion. However as Dr Glaser has shown, echocardiographic demonstration of MAC should not pose a *diagnostic* problem in patients with massive pericardial effusion. His report of MAC in chronic dialysis patients with secondary hyperparathyroidism is of additional clinical interest because of the potential for infection on the mitral ring.

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Book reviews

Clinical Cardiology. Edited by James T. Willerson, M.D., F.A.C.C., and Charles A. Sanders, M.D., F.A.C.P., F.A.C.C., New York, 1977, Grune & Stratton, Inc., 660 pages. Price $39.50.

This book edited by Willerson and Sanders, is brief description of cardiac diseases in which the contributors have emphasized the pathophysiologic relationship to clinical disease states. The use of graphic recordings such as cardiac angiography, echocardiography, arteriography, radioisotopic scanning, and others are prominent in the various discussions. There apparently is an effort to include the new concepts that are not fully accepted or established as worthwhile. For example, on pages 367 and 368, the use of glucose-insulin-potassium solution is recommended to "reduce infarction size." It is this reviewer opinion that the term "infarction" means death of tissue due to arrest of the circulation. Therefore, how can anyone reduce infarct size. That would mean creating or re-establishing life. And, that is not possible. Such careless statements are not advisable for textbook. Surely this reviewer realizes that the author means treatment of infarcts designed to prevent myocardial infarcts from enlarging or to keep them small. Another point worth noting is to consider ischemia and anoxia as being synonymous when discussing ischemic heart disease. The ischemia of coronary heart disease means reduced supply of circulating blood. Blood carries more than oxygen to the tissues that are necessary for cellular metabolism and the blood also removes waste products of metabolism, not only CO_2. Such careless writing needs improvement in future editions.

The book does correlate the modern approach to clinical cardiology in which expensive and even dangerous graphic procedures are employed. Most of these are unnecessary. However, those who employ this approach will appreciate this book. The book is good one and it certainly defines very well present day clinical cardiology as practiced in the large medical centers. Students, housestaff, and physicians will find many important, useful, and interesting concepts in this book. It must be read thoughtfully. Like all such books, it does not completely review all aspects of clinical cardiology. The practicing bedside clinicians will find this book to be difficult to read and understand.

Current Cardiovascular Topics. Vol. IV. Acute Myocardial Infarction. Edited by Ephraim Donoso, M.D., and Janet Lipski, M.D., New York, 1978, Stratton Intercontinental Medical Book Corporation, 270 pages. Price $37.50.

This volume of *Current Cardiovascular Topics on Acute Myocardial Infarction* is intended for clinicians who manage myocardial infarction. The book is well organized. It includes 14 chapters which discuss the conduction system, coronary care units, immediate management, the electrocardiogram, treatment of arrhythmias and myocardial regional dysfunction, pathology, use of anticoagulants, surgical care, post hospital care, and even such an esoteric subject as ST segment mapping. This is good review of the clinical care of acute myocardial infarction for the practicing physician. The book is worth owning and deserves careful study.

Atlas of Cardiovascular Nuclear Medicine. Selected Case Studies. By H. William Strauss, M.D., Bertram Pitt, M.D., Jacques Rouleau, M.D., Ian K. Bailey, M.B., and Henry N. Wagner, M.D., Saint Louis, 1977, The C. V. Mosby Company, 194 pages. Price $42.50.

This atlas includes selected case studies that illustrate effectively the application of uclear medicine to the evaluation of cardiovascular problems. The use of radio elements in clinical cardiology has little application when it is realized that other standard special procedures already provide the services needed for the study of cardiac disease states. Nevertheless, there is emphasis these days on the use of nuclear medicine in clinical cardiology in spite of its limited usefulness. The need for research in this field is recognized, and this deserves support. This atlas does summarize very well with well selected illustrations the applications of nuclear medicine to cardiology as is presently practiced. Readers will find this to be a good source for study of the subject.

Cardiac Arrhythmias: Exercises in Pattern Interpretation, second edition. By Mary H. Conover, R.N., B.S., St. Louis, 1978, The C. V. Mosby Company, 267 pages.

This manual on cardiac arrhythmias, written by a nurse trained in critical care, is intended for nurses and others who assist physicians in the care of critically ill patients. This publication is primarily an atlas of representative short strips of electrocardiograms which reveal common disturbances in cardiac rhythm that might be encountered in intensive care units, coronary care units, and emergency rooms. The manual is good one and the tracings are well selected. This is not publication intended to teach the fundamentals of electrocardiography nor is it intended for physicians or medical students. This second edition should continue to serve good function in training nurses and other paramedical attendants who are responsible for the care of seriously ill patients.

specific and age-specific mortality from CHD The degree of risk connected with a particular risk factor is often defined in terms of a *mortality ratio* which usually varies with age. (A *mortality ratio* is given by the death rate from the disease in question in persons with the risk factor divided by the corresponding death rate in a suitably matched group of persons without the factor) Mortality ratios for CHD decrease with increasing age for cigarette smoking, excess relative weight, hypertension, diabetes, and hypercholesterolemia. By contrast, when non-exercisers are compared with heavy exercisers, the mortality ratio *rises* with increasing age.

Also of theoretical importance is the relation between the mortality ratio and, for example the rate of cigarette smoking within a given age group. Whereas this relation is approximately linear for bronchitis and lung cancer we find for CHD that, after an initial rise that appears to be more or less linear a near plateau is reached at a smoking rate of about 20 cigarettes per day especially in the higher age groups.

To achieve a satisfactory synthesis the over all evidence—epidemiological, observational, and experimental—needs to be accommodated within a unifying framework. Because risk factors are usually identified from epidemiological evidence we have to ensure that it is exploited as rigorously as possible.

Age-dependent disease, theory

The various associations between risk factors and CHD receive a simple interpretation in terms of a unified theory of growth, cytodifferentiation, and age-dependent *autoaggressive* disease. This unified theory derives in part from Burnet's forbidden clone concept of disturbed tolerance autoimmune disease and also from Burwell's view that the growth of target tissues throughout the body is regulated by components of the lymphoid system. A brief description of the pertinent features of the unified theory will suffice to explain the different types of association between risk factors and CHD

To become the victim of a specific autoaggressive disease a person must first possess a specific genetic predisposition. Occasionally diathesis takes the form of a simple autosomal dominant or recessive inheritance, but more commonly polygenic predisposition is involved. In that event, the chance of one polygenic disorder being associated with another may become appreciable; numerous recent studies have revealed the complexities of the associations not only between one disease and another but also between diseases and the major histocompatibility antigens. These latter associations, predicted by us, make the genetic basis explicit. If, therefore we study a group of persons with a specific genotype—say maturity-onset diabetics—the proportion of persons predisposed to CHD in this selected group may well differ from that in the general population. The genes that predispose to maturity-onset diabetes mellitus might associate, positively or negatively with those that predispose to CHD Furthermore, the type and strength of the association might well differ from one population to another

But given a genetic predisposition to CHD many years usually elapse before the disease develops: the risk of death from CHD small at the age of 20, increases very steeply with age. One of our main tasks is to describe, in biological terms, the striking characteristics of this steep age-dependence.

From studies of hundreds of age patterns, relating to many types of disorder an unexpectedly simple and unified interpretation has emerged. The kinetics of the disease process can be divided into two distinctive phases: *initiation* and *development*. (In certain diseases—neoplastic and non-neoplastic—qualitatively distinctive stages of *progression* can also be distinguished but this phenomenon need not detain us here; it has been analyzed elsewhere.)

Initiation is a purely random process involving the occurrence of a specific set of spontaneous somatic gene mutations in one or more central growth-control stem cells. In the example of fatal CHD it appears that six somatic mutations need to occur in a single growth-control stem cell to complete the process of initiation. The steep age-dependence of CHD—age-specific initiation rates increase with the fifth power of age up to about 75 years of age—is a consequence of this multi-step random (stochastic) process. I have seen no indication that extrinsic pathogens, at the levels encountered in ordinary environments, have any detectable influence on the rate of occurrence of the initiating somatic mutations in CHD or any other autoaggressive disease. However different rates are often observed between, for example, Caucasoid and Japanese populations and they presumably have a genetic basis.

On completion of initiation the appropriately mutant stem cell propagates a forbidden clone of descendant cells, the peripheral members of which, in the example of CHD probably comprise T lymphocytes. These mutant T lymphocytes attack specific target cells (perhaps particular mosaics of endothelial cells) that carry complementary recognition proteins. When damage to the target tissue reaches a certain level, death ensues. We describe the process from the formation of the forbidden clone to death as the *development* phase we call its duration the *latent period*. In general, the development process may be affected by extrinsic factors—causal and therapeutic—but its average duration is dominated by genetic inheritance. In the England and Wales and the United States "White" populations the average latent period for CHD is 10 years in males and 20 years in females; in the United States "Blacks" the corresponding intervals are only 5 and 10 years, respectively However this latter disadvantage is more than compensated by the fact that a smaller proportion of "Blacks than of "Whites is at genetic risk to CHD (It should be mentioned that CHD belongs to a general class of autoaggressive disease in which the average latent period in women is double that in men in another class the average latent periods are the same in both sexes.)

Risk factors: the nature of the association with CHD

Analysis of suitably accurate sex-specific and age-specific death rates for a sub-population of persons, selected as possessing a particular risk factor enables the nature of the association between risk factor and CHD to be determined. With cigarette smoking, relative weight and, probably hypercholesterolemia, the association in each instance is only with the duration of the latent period. Thus, in non-smoking United States males, the average latent period for non-smokers is 15 years, but the interval shortens progressively to 5 to 6 years for those smoking 20 (or 21) to 39 cigarettes a day· and to 3 to 4 years for those smoking 40 or more cigarettes a day Among United States women this inverse association between latent period and smoking rate is weaker· in non-smokers the duration is 24 years and for those smoking 20 to 39 cigarettes a day it is 18 years.

For the risk factors hypertension, diabetes mellitus, and lack of voluntary exercise, the association with CHD has a dual basis. In the first place, hypertensives, diabetics, and non-exercisers are more likely to be genetically predisposed to fatal CHD than "normal" controls. The second aspect of the association between these particular risk factors and CHD involves the latent period. In hypertensives and diabetics the latent period is shorter than in the general population but in non-exercisers it is longer This latter phenomenon explains why the mortality ratio for non-exercisers versus heavy exercisers increases with age, whereas for all the other risk factors analyzed[a] it decreases.

Are the associations causal?

The findings and interpretation in connexion with exercise raise a particularly interesting and important issue. A heavy exerciser is 3.3 times less likely to be genetically predisposed to fatal CHD than a non-exerciser and exercise has no effect on the initiation of a forbidden clone by random somatic mutation. However once the forbidden clone has been initiated, the latent period is markedly shorter (5 years for men, 18 years for women) in the heavy exerciser than in the non exerciser (10 years for men, 24 years for women). If this shortening of the latent period is *caused* by strenuous physical exertion then heavy exercise (or even moderate and slight exercise) should be regarded as a risk factor in those persons that are unfortunate enough to have an initiated forbidden clone. Although the over-all evidence, showing an effectively constant latent period both in time and with age, favors a genetic interpretation of the connection between latent period and the degree of exercise (especially voluntary) I am unaware of any evidence that bears directly and decisively on the problem.

Overwhelmingly important in view of the social and political consequences generated by enthusiasm for preventive medicine is the *cause* of the short latent periods in cigarette smokers, hypertensives, the obese, and in persons with hypercholesterolemia. Fortunately where smoking is concerned, the properties of the age-dependence of mortality from CHD and of the secular trends (1921 to 1973) in sex-specific and age-specific death rates, enable reasonably confident conclusions to be drawn. (Seltzer[11] has given independent reasons for doubting the causal interpretation.) If the short latent period is caused by the

smoking then (1) the post 1921 changes (mainly increases) in cigarette smoking in England and Wales should have generally shortened the latent period in both sexes, (2) because the average rate of smoking decreases with increasing age above about 55 years of age the latent period in older men and women should be longer than in younger persons. The Registrar General s mortality statistic fail to confirm either expectation. Although large increases have been recorded in death rates from CHD and although changes in the International Classification of Diseases have introduced some interpretational difficultes, the data give no indication of any systematic shifts in the latent period between 1921 and 1973. Over the age range yielding the most reliable and consistent data (below about 75 years of age) the average latent period has remained close to 10 years in men and 20 years in women throughout the era.

We could always argue that, although cigarette smoking has generally increased in the post 1921 era, especially in women, other causal factors affecting the latent period have decreased so as to compensate for the adverse effects of tobacco. Until such hypothetical agents—with their requisite and improbable time variation and their equally improbable sex and age dependence—can e identified, such arguments must be regarded as uspect to the point of absurdity

The consumption of foods such as eggs, fatty meat milk, and dairy products that are supposed to raise serum cholesterol levels has also changed since 1921 the changes have generally been increases, although from 1970 to 1976 total fat, butter and total egg consumption decreased, Because the latent periods have failed to reflect these secular trends, the hypothesis that dietary cholesterol causes CHD is not supported. McMichael[14] and Mann have also given reasons for rejecting this hypothesis.

Hypercholesterolemia, obesity and hypertension all increase in prevalence with age and the finding of effectively constant latent periods for CHD with age indicates that none of these conditions causes CHD

Nevertheless, the large increases in recorded death rates (about a factor of 15 between 1921 to 1925 and 1971 to 1973, depending slightly on age group) remain to be accounted for There is little doubt that at least some part of these increases can be ascribed to better recognition of the disease the mathematical characteristics of the age patterns throughout the era indicate that the degree of under recognition, up to the age of about 75, was very similar in the two sexes. However these same mathematical characteristics allow another general type of interpretation. They are consistent with the idea that part of the recorded increase was genuine and caused by a *precipitating* factor that increased in prevalence in the course of the century and acted uniformly on men and women of all ages. A *precipitating* factor of which infective microorganisms and allergens are the best known examples, is an extrinsic agent that releases an initiated forbidden clone from restraints that are normally exercised by the host s endogenous defence mechanism. No evidence for such a factor has yet been uncovered in connection with CHD but should it transpire that part of the secular increase in recorded death rates is genuine, and not merely the result of better ascertainment, then search for such an agent might prove rewarding.

In spite of the consensus among many experts, the secular increases and age-dependence of recorded death rates from CHD cannot plausibly be reconciled with the view that cigarette smoking, consumption of cholesterol-containing foods, hypertension, obesity and diabetes actually *cause* the disease. The evidence indicates that for each of these "risk factors the observed associations, with all their subtle but readily interpreted features, have a genetic basis. This is probably true also of exercise, although as yet it cannot be conclusively ruled out that physical exertion might *hasten* death from CHD

If this analysis is substantially correct it follows that intervention programs—unless they involve by accident or design a reduction in the purely hypothetical and unidentified precipitating factor—are not only doomed to disappointment, they are likely to create unnecessary misery and anxiety And what should one say about a publication,[16] in a highly reputable journal, in which the economic consequences of smoking and alcohol abuse" are calculated to six *(sic)* significant figures?

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Clinical communications

Echocardiographic diagnosis of pericardial disease

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In an earlier prospective evaluation of pericardial effusion in patients undergoing open heart surgery parallel moving echoes with a clear space between them were noted in the region of the posterior pericardium in two patients with surgically confirmed pericardial fibrosis without associated pericardial effusion. Thirty nine other patients with effusion but without this ultrasonic pattern of pericardial fibrosis did not have surgical evidence of pericardial thickening. The present report is an extension of these findings in patients with suspected constrictive pericarditis.

[Pati]ents and methods

Echocardiograms were performed prior to cardiac catheterization in six patients with constrictive pericarditis and in five patients with effusive-constrictive pericarditis. Catheterization evidence of restrictive or constrictive disease was considered present when there was end-diastolic equalization of all recorded intracardiac pressures to within 6 mm. Hg. Pericardiectomy was performed under cardiopulmonary bypass in all 11 cases. The parietal pericardium was stripped between the phrenic nerves anteriorly. In two cases, additional pericardium posterior to the phrenic nerves was resected. If the visceral pericardium was found to be thickened, this visceral peel also was resected. Gross and microscopic evaluation of the surgical specimens was performed in all cases. A Smith Kline Ekoline 20A Ultrasonoscope and a strip-chart recording of the M mode sector scan was used in each case. The technique for recording the pericardium and its movement used in this laboratory was previously described. Each echocardiogram was individually evaluated for the presence of pericardial effusion by two of the authors. Also, the posterior pericardial area was inspected for a space between the dominant high intensity echo taken to represent the parietal pericardial, pleural, pulmonary interface and echoes anterior to it. The motion of the parietal pericardial echoes was noted relative to the myocardial echoes.

Results

Anatomic evidence of pericardial disease was found in each case and the operative findings are discussed below.

Three general echocardiographic patterns of pericardial thickening were noted. These patterns were related to the pericardial pathology but are segregated for illustration and possible clinical implications (see Table I).

Chronic pericardial fibrosis without effusion was associated with two parallel moving echocardiographic lines with a clear space between them, reflected from the region of the posterior pericardium. These lines persisted during marked damping and/or low amplification of the ultrasonoscope (Fig. 1). This implies marked differences in density of tissue compared to the rest of the cardiac echoes in this area. In some cases, the two parallel lines were not always equally dense and persistent during maximal damping. Then only

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Table I Pathologic and echocardiographic correlations

Pericardial pathology	Echocardiography
1. Pericardial fibrosis or Pericardial calcification	1. Intense parallel moving echoes separated by small echo-free space or single dense band of echoes
2. Effusive-constrictive disease. Liquid pericardial effusion and thickened visceral and parietal pericardia	2. Posterior echo-free space representing the liquid pericardial effusion and parallel moving multiple echoes or dense thick band of echoes from the region of the thickened visceral pericardium
3. Fibro-elastic or dry pericarditis. Spongy coagulated pericardial exudate and thickened parietal and visceral pericardia	3. Numerous random echoes from the region between the visceral and parietal pericardia during minimal damping and a relatively clear space during maximal damping. These random echoes represent the coagulated pericardial exudate. Reduced motion of the parietal pericardium relative to the visceral pericardium. Parallel echo lines or dense echo band from the thickened visceral and/or parietal pericardia

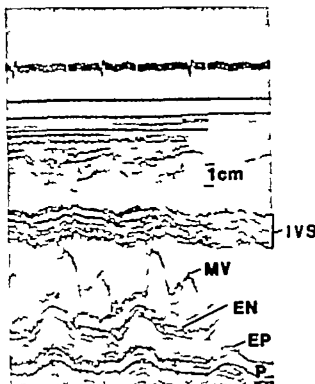


Fig. 1 The echocardiogram from patient shown to have chronic pericardial fibrosis without associated pericardial exudate at surgery. Parallel moving lines with clear space between them were reflected from the posterior pericardium and persisted during maximal as well as minimal damping. Maximal damping is seen *in the right portion* of the panel near the labels. *IVS* = interventricular septum, *MV* = mitral valve apparatus; *EN* = endocardium, *EP* = epicardium and visceral pericardium, *P* = parietal pericardium.

the more posterior ultrasonic signal persisted one to eight millimeters from the more anterior signal recorded with slightly less damping (Fig. 2). Fig. 3 shows pre- and postoperative echocardiograms from a patient whose resected pericardium is shown in Fig. 4. The surgical specimen shows fibrotic tissue, ranging from one to four millimeters in thickness. The variability of thickness was noted as variable echocardiographic separation of the parallel posterior echoes observed in M mode sector scans of the heart.

Effusive-constrictive pericarditis[a] or subacute wet pericarditis was associated with a posterior echo-free space of pericardial effusion, and in addition multiple dense parallel moving echoes from the region of the thickened visceral pericardium were seen. Fig. 5 shows this combination of findings. Following pericardiocentesis, there was a marked decrease in the size of the posterior echo-free space while the multiple parallel echoes from the region of the thickened visceral pericardium remained. The surgical specimen of the visceral pericardium is shown in Fig. 6. In some cases of effusive-constrictive disease, the posterior echo-free space was obvious but the thickened visceral pericardium was represented by only a single band of dense echoes. Although such a dense band of echoes was seen with visceral pericardial thickening, the increased intensity of these echoes was subjective and dependent on optimal adjustment of the equipment.

A third echocardiographic pattern was associated with a form of dry pericarditis. This represents a stage, or type of pericardial disease intermediate between the two types just mentioned. A finite distance existed between the intense posterior visceral and parietal pericardial echoes. Numerous ultrasonic signals filled this space during minimal damping while the space usually cleared somewhat during maximal damping. The



Fig. 2. Echocardiogram from patient in a previously reported study with chronic pericardial fibrosis without associated pericardial exudate at surgery Parallel moving echoes reflected from the posterior pericardium during minimal damping. Only the most posterior pericardial echo remained during maximal damping t the gain setting. C = chordae tendineae. Other abbreviations as in *Fig. 1*

posterior parietal pericardial echoes often showed y less motion than the visceral pericardial echoes (Fig. 7). This comparative movement was in contrast to the nearly equal, or parallel, motion of the echoes returning from the severely fibrosed pericardium of patients with longstanding chronic pericarditis in this series. This third echocardiographic pattern of dry pericarditis also was present following pericardiocentesis in cases of effusive–constrictive disease.

Pathologic evaluation of pericardia from patients with this third echocardiographic pattern showed results that were intermediate between the cases with densely fibrotic material in the pericardial space without any pericardial effusion and cases *with effusive–constrictive* disease. In this intermediate form, spongy coagulated pericardial exudate was adherent to the thickened parietal pericardium and/or to the thickened visceral pericardium (Fig. 8) The cases of effusive–constrictive disease showed similar pathology after removal of the liquid pericardial *contents.*

Motion of the interventricular septum was variable. Of the six patients with constrictive pericarditis, four had echocardiograms which showed normal interventricular septal motion *(See Figs 2 and 3)* while two patients exhibited paradoxical septal motion. From the five patients with effusive–constrictive disease, there was one echocardiogram with normal septal motion, one with paradoxical septal motion, and three with reduced but neither normal nor paradoxical septal motion.

Septal thickening during systole was determined by finding the difference between septal thickness at end-systole and end-diastole and dividing by the end-diastolic thickness. The range of per cent systolic septal thickening in normal patients was found to be 30 to 65 per cent. *Among the eleven patients in this study* with constrictive pericarditis and effusive–constrictive disease, the mean per cent systolic septal thickening was found to be 26 ± 4 per cent with a range of 18 to 45 per cent. Six other patients with restrictive cardiomyopathy demonstrated a marked reduction of systolic septal thickening with a mean of 5 ± 3 per cent and a range of 0 to 11 per cent. The difference between the 11 patients with surgically remediable constrictive pericarditis and the six other patients with restrictive cardiomyopathy was highly significant ($P < 0.01$)

Discussion

Pericardial pathology was associated with three echocardiographic patterns. These patterns represented three types of pericardial pathology (1) chronic, long-standing pericardial fibrosis, (2) effusive–constrictive, wet pericarditis, and (3) dry or fibroelastic pericarditis.[6]

Chronic pericardial fibrosis, without liquid effusion or coagulated pericardial exudate, was associated with two parallel moving ultrasonic lines, separated by a distance of one to eight millimeters (Fig. 1) Since the lower limit of axial resolution of returning signals from the 2.25 MHz *transducer and this ultrasonoscope was* approximately one millimeter the pathologic pericardium must be at least one millimeter in thickness to produce the two distinct ultrasonic signals. A single strong acoustical interface may produce subsequent reverberations of less intensity which could simulate the parallel ultrasonic lines of pericardial thickening. Increased *damping or* reduced gain settings tend to suppress reverberations and better define each primary sound reflecting interface. Persistence of these parallel

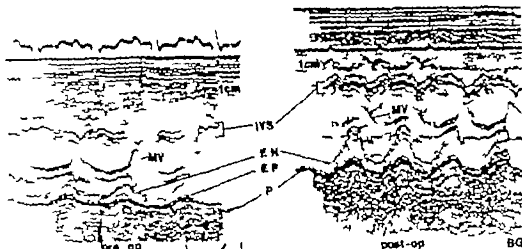


Fig. 3. Pre- and post-pericardiectomy echocardiograms from a patient with surgically proven pericardial fibrosis. *The echo labelled EP* (epicardium or visceral pericardium) is not as intense as *the echo labeled P* (parietal pericardium) although these echoes are separated by 4 mm. in the preoperative period.



Fig. 4. Surgical specimen showing variable thickness of the fibrotic pericardium from the same patient as *Fig. 3.*

lines with a definite echo-free space between them despite near maximal damping reduces the practical problem of spurious ultrasonic signals giving this pattern. A very dense echo followed by less intense echoes moving in parallel should be interpreted with caution nevertheless.

In some cases, and in various areas of the same heart, maximal damping suppresses the more anterior visceral pericardial echo while allowing the persistent recording of the more posterior parietal pericardial echo (Fig. 2). Although this latter pattern alerts us to search for two equally intense echoes, it may not be as specific as the persistent equally intense parallel lines shown in Fig. 1. Parallel movement of these pericardial echoes reduces the probability of liquid pericardial effusion which usually insulates the parietal pericardium from myocardial motion.[1, 16]

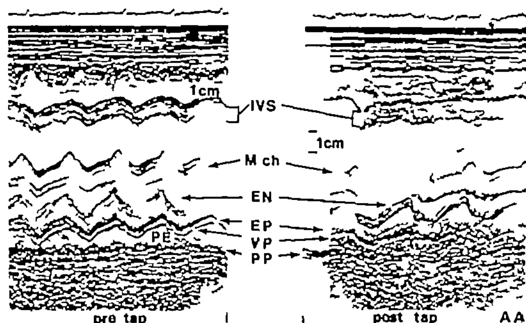


Fig 5. Echocardiograms before (left) and after (right) pericardiocentesis from patient with subacute effusive-constrictive pericarditis. Following pericardiocentesis, the echo-free space decreased while the parallel lines from the thickened visceral pericardium remained.



Fig. 6 Surgical specimen from the case shown in Fig. 5. Note the thickening of the visceral pericardium.

The occurrence of coagulated pericardial exudate adherent to the parietal or the visceral pericardium was noted before[4] (Fig. 8) This pathology may create a fibroelastic type of constriction and impair ventricular filling.[4, 6] Although a relatively clear space between visceral and parietal pericardium may be evident on the echocardiogram during maximal damping, numerous signals fill this space during intermediate or minimal damping (Fig. 3) This may be due to multiple fluid tissue interfaces in this spongy tissue. This spongy exudate may alter the movement of the parietal pericardium relative to the visceral pericardium and myocardium. Thus, this pattern may be difficult to differentiate from a small liquid pericardial effusion on the echocardiogram. However the appearance of numerous signals in the presumed

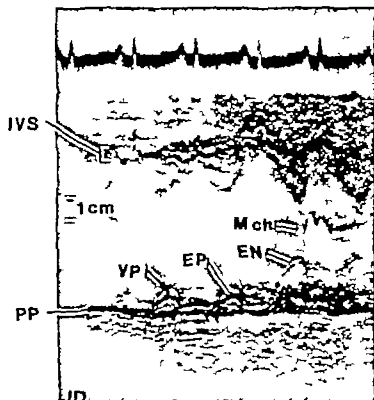


Fig 7 Echocardiogram from patient with subacute dry pericarditis. The pattern of epicardial and pericardial motion is similar to simple liquid effusion. However numerous random echoes fill the small space between the epicardium and the relatively flat posterior parietal pericardium.

pericardial space during minimal or intermediate damping and the presence of dense or parallel multiple lines from the region of the thickened visceral or parietal pericardium may help to differentiate this condition from a simple small liquid effusion.

Effusive–constrictive pericarditis was characterized by a posterior echo-free space representing the liquid pericardial effusion and parallel moving multiple lines or a very dense thick band of echoes from the region of the visceral pericardium in our patients (Fig. 5). This was confirmed by a decrease in the echo-free space following pericardiocentesis, while the parallel multiple or single dense band of echoes from the visceral pericardium remained. The post-pericardiocentesis echocardiogram in such cases resembled the echocardiograms from patients with the intermediate dry form of pericarditis.

These echocardiographic patterns probably represent the continuum of pericardial pathology. Subacute pericarditis may be wet and associated with liquid pericardial effusion, or dry and associated with coagulated pericardial exudate.[1-4] In both types of subacute pericarditis, the pericardium is diseased and thickened. Ultimately the pericardial exudate may resolve with formation of dense adhesions between the visceral and parietal layers of the pericardium. This may give rise to the thick layer of constricting fibrous tissue found in chronic pericarditis.

Echocardiographic evaluation of the interventricular septum may be helpful in differentiating restrictive cardiomyopathy from constrictive per icarditis. Since constrictive pericarditis is a disease which primarily affects the external cardiac structures such as the pericardium and epicardium, internal cardiac structures such as the interventricular septum should be relatively free of disease. In contrast to constrictive pericarditis, restrictive cardiomyopathy is not limited to the cardiac surface but generally involves the interventricular septum as well as the free walls of the left and right ventricles. Using per cent systolic septal thickening to quantitate septal contractility it was possible to show a highly

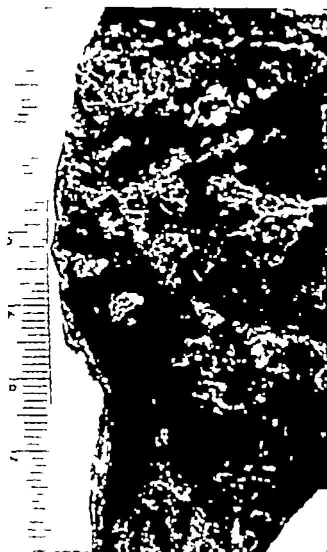


Fig 8. Surgical specimen from the case shown in Fig 7 demonstrating coagulated pericardial exudate adherent to the thickened parietal pericardium.

significant difference between the 11 patients with constrictive pericardial disease and six other patients with a restrictive myopathy Per cent systolic septal thickening was near normal in the patients with constrictive pericaridal disease 26 ± 4 per cent, while it was markedly reduced in the patients with restrictive cardiomyopathy 5 ± 3 per cent (P < 01)

Other authors found that an abnormality of septal motion was characteristic of constrictive pericarditis.[1,2] The patients in this study showed variable and non-diagnostic motion of the interventricular septum. The number of patients in this series was small and a large series may provide a definitive answer regarding septal motion and constrictive pericardial disease.

Although the echocardiogram may suggest that pericardial thickening is present, this does not denote hemodynamically significant constriction. The patterns of subacute pericardial thickening or fibrotic pericardial thickening are seen commonly after cardiac surgery in which the pericardium is opened. Obviously not all material which accumulates within the pericardial space goes on to cause cardiac constriction. Further investigation is ongoing to search for reliable echocardiographic evidence of restricted ventricular filling and to address the clinical problem of separating constrictive pericarditis from restrictive myopathy

Summary

Echocardiograms were performed in 11 patients with constrictive pericarditis or effusive-constrictive pericarditis confirmed by cardiac catheterization and pericardiectomy Three echocardiographic patterns of pericardial disease were noted and were related to three types of pericardial pathology Parallel moving echoes separated by a clear space were reflected from chronically fibrosed and thickened pericardium without associated pericardial exudate Effusive-constrictive pericarditis or subacute wet pericarditis was characterized on the echocardiogram by a posterior echo-free space representing the liquid pericardial effusion and multiple ultrasonic lines from the thickened visceral pericardium. Subacute dry pericarditis was associated with numerous ultrasonic signals filling the space between the visceral pericardium and the relatively flat parietal pericardium. These ultrasonic signals were reflected from coagulated pericardial exudate which was adherent both to the parietal pericardium and the visceral pericardium. Parallel moving echoes or dense bands of echoes were reflected from either or both thickened visceral and parietal pericardium.

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HL A and hypertrophic cardiomyopathy

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Idiopathic cardiomyopathy defined as "a disorder of heart muscle of unknown cause or association,"[1] has been the subject of intense investigation over the years. It is classified into hypertrophic (with or without obstruction) and congestive types, based on functional pathology. Previous studies have indicated that hypertrophic cardiomyopathy is often familial and genetic factors were considered in the pathogenesis of the disease.

Recently several antigens of the HL-A system have been noted in association with diseases thought to have an immunological basis and in which there is a high familial incidence.

We investigated HL-A antigens—the human major histocompatibility complex—in patients with hypertrophic cardiomyopathy.

Methods

Twenty-six unrelated Japanese patients with hypertrophic cardiomyopathy were included in the study. There were 17 males and nine females and ages ranged from 15 to 51 years (average, 35 years). In 22 cases, the diagnosis was established by cardiac catheterization with angiocardiography. In nine patients, endomyocardial biopsy was performed. In the other four cases, the diagnosis was confirmed by echocardiographic findings of asymmetrical septal hypertrophy (septal posterior left ventricular wall thickness ratio ≥1.3 and septal thickness ≥1 4 mm.) Fifteen patients had obstruction of the left ventricular outflow and there was no obstruction in 11 patients.

HL-A typing was performed by a lymphocytotoxicity micromethod.[a] Seventy antisera were used to define 21 major HL-A specificities. Sera were prepared at Tokai University. The antigens typed for were HL-A A1 2,3,9,10 11,28, and AW19 of the A series; HL-A B5 7,8,12,13,15 and BW16,17,21,22,35,37 and 40 of the B series.

HL-A antigen frequencies in 26 patients were compared with those in 176 controls and the significance of difference was determined by χ^2 test, using Yate's correction for small samples.

We also determined the HL-A types in two families in which many members were affected. All available family members underwent complete histories, physical examinations, electrocardiograms and echocardiograms.

Results

Several HL-A antigens were more common in patients but there was no significant difference in frequencies of HLA antigens between patients and controls (Table I).

Of 26 patients, six were confirmed to have at

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least one first-degree relative with hypertrophic cardiomyopathy In three of these six families, the probands had HL-A A9 and B7 In the other three, the probands had HL-A A2 and BW35.

Family 1 (Fig 1) The proband was a 41 year-old woman. The diagnosis of hypertrophic cardiomyopathy without obstruction was established by cardiac catheterization. Her mother and younger brother had marked ST T abnormalities of the electrocardiograms and hypertrophic cardiomyopathy was confirmed by echocardiograms.

Genetic analysis showed that the proband carried the HL-A A9,B7 haplotype. This haplotype was also found in her mother and a brother both affected. On the other hand, her father and elder brother not carrying the HL-A A9,B7 haplotype, showed no cardiac abnormality The proband s child, aged 10 years, had the HL-A A9,B7 haplotype, and an inverted *T* wave through Leads V to V was seen on the electrocardiogram, but echocardiographic abnormalities were not evident.

Family 2 (Fig 1) The proband was a 39-year-old woman. The diagnosis was hypertrophic cardiomyopathy without obstruction. Her mother had cardiac asthma" and suddenly died at the age of 43. Cardiomyopathy was suspected. The younger sister 36 years old, also underwent cardiac catheterization in another hospital and was diagnosed as a case of hypertrophic cardiomyopathy without obstruction. Her brother 33 years old, had systolic hump as determined by echocardiography and was diagnosed as hypertrophic cardiomyopathy with obstruction.

All the affected members shared HL-A-A9 and B7 On the other hand, the youngest sister (26 years old), the proband s child, and a child of an affected sister all of whom had no cardiac abnormalities, did not share HL-A B7 The HL-A A9,B7 haplotype may therefore be associated with the occurrence of the disease in this family

Table I Percentage frequency of 21 histocompatibility antigens in 26 patients with hypertrophic cardiomyopathy and in 176 controls

Antigen	*Patients n = 26 (%)*	*Controls n = 176 (%)*
HL-A-A1	0	0
A2	53.8	47.2
A3	0	0
A9 (AW24)	61.5	53.4
A10 (AW26)	34.6	19.9
A11	11.5	15.9
A28	0	0
AW19	11.5	19.3
HL-A-B5	30.8	34.7
B7	15.4	8.0
B8	0	0
B12	7 7	17.6
B13	7 7	4.5
B15	11.5	18.2
BW16	3 8	10.2
BW17	7 6	0 6
BW21	0	0
BW22	19.2	19.3
BW35	34.6	19.3
BW37	0	0
BW40	34.6	36.2

Discussion

The etiology of idiopathic cardiomyopathy is unknown. In hypertrophic cardiomyopathy however high familial occurrence and autosomal dominant traits have been documented. Braunwald and colleagues[4] reported that familial incidence accounted for approximately 30 per cent, and Clark and associates[5] using echocardiography detected familial occurrence of asymmetrical septal hypertrophy in 28 of 30 families. An autoimmune mechanism may indeed be involved in the pathogenesis of some of the patients with cardiomyopathy but there is apparently no direct evidence to implicate a virus or immunological mechanisms in initiation and pathogenesis of the disease.

Recent studies revealed that several HL-A antigens were associated with the diseases considered to have an immunological basis and in which there is a high familial incidence.

In our present work, we found no significant differences in frequency of HL-A antigens between patients with hypertrophic cardiomyopathy and the controls. Family studies, however revealed a close association of the HL-A haplotype with the occurrence of hypertrophic cardiomyopathy In Family 1, the proband was HL-A A9,B7 The disease occurred only in the family members who carried the HL-A A9,B7 haplotype and not in the others. In Family 2, all the affected family members seemed to share the HL-A A9,B7 haplotype. None of the unaffected members had HL-A B7 In these families, six of seven kindred

HL A and hypertrophic cardiomyopathy

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Idiopathic cardiomyopathy defined as "a disorder of heart muscle of unknown cause or association,"[1] has been the subject of intense investigation over the years. It is classified into hypertrophic (with or without obstruction) and congestive types, based on functional pathology. Previous studies have indicated that hypertrophic cardiomyopathy is often familial and genetic factors were considered in the pathogenesis of the disease.[2]

Recently several antigens of the HL-A system have been noted in association with diseases ought to have an immunological basis and in there is a high familial incidence.

We investigated HL-A antigens—the human major histocompatibility complex—in patients with hypertrophic cardiomyopathy.

Methods

Twenty-six unrelated Japanese patients with hypertrophic cardiomyopathy were included in the study. There were 17 males and nine females and ages ranged from 15 to 51 years (average, 35 years). In 22 cases, the diagnosis was established by cardiac catheterization with angiocardiography. In nine patients, endomyocardial biopsy was performed. In the other four cases, the diagnosis was confirmed by echocardiographic findings of asymmetrical septal hypertrophy (septal-posterior left ventricular wall thickeness ratio ≧1.3 and septal thickness ≧14 mm.). Fifteen patients had obstruction of the left ventricular outflow and there was no obstruction in 11 patients.

HL-A typing was performed by a lymphocytotoxicity micromethod.[3] Seventy antisera were used to define 21 major HL-A specificities. Sera were prepared at Tokai University. The antigens typed for were HL-A A1, 2,3,9,10,11,28, and AW19 of the A series, HL-A B5,7,8,12,13,15 and BW16 17,21,22,35,37 and 40 of the B series.

HL-A antigen frequencies in 26 patients were compared with those in 176 controls and the significance of difference was determined by χ^2 test, using Yate's correction for small samples.

We also determined the HL-A types in two families in which many members were affected. All available family members underwent complete histories, physical examinations, electrocardiograms and echocardiograms.

Results

Several HL-A antigens were more common in patients but there was no significant difference in frequencies of HLA antigens between patients and controls (Table I).

Of 26 patients, six were confirmed to have at

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may play some role in the pathogenesis of hyper trophic cardiomyopathy with familial occur rence.

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Noninvasive assessment of myocardial function in young patients with mitral valve prolapse

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Several investigators[1] have described abnormalities of the left ventricular contraction pattern in patients with mitral valve prolapse (MVP). Gulotta and colleagues found significant impairment of left ventricular contractility in all of his 26 patients studied. Gooch and associates[2] observed asynergistic contractions or relaxations in 70.8 per cent of 24 patients. In a study on 87 patients, Scampardonis and co-workers[3] found abnormal left ventricular systolic contraction patterns but noticed that over all left ventricular performance was normal generally. However this study was done at rest. The nature of these abnormalities remains unknown. ... authors have speculated about the existence of a cardiomyopathy or of a papillary ...le dysfunction secondary to ischemia. In view of the discrepant findings relating to myocardial function and in view of the high prevalence of mitral valve prolapse[4-] we examined mild cases of this disorder noninvasively. In addition, we wanted to find out whether exercise can reveal latent myocardial dysfunction.

Patients and methods

Fourteen patients (six men, eight women) aged 28 ± 6.3 years were investigated. Thirteen of them had MVP documented by typical echocardiographic features while one patient exhibited only a mid-systolic click and a late-systolic murmur. Patients with associated coronary artery disease or atrial septal defect and patients with evidence for significant mitral regurgitation were not included in the study. Pertinent clinical data are summarized in Table I.

Systolic time intervals (STI) were recorded at rest both in the supine (n = 14) and in the upright position (n = 13) in the way previously described by Weissler and associates. In seven additional patients STI were determined after bicycle ergometry (3 minutes at 50 W and 3 minutes at 110 W) in the upright position. Recordings were made on a six-channel recorder type "Hellige Multiscriptor EK 22" at a paper speed of 100 mm./sec. All tracings were coded with random numbers and were interpreted by two blinded investigators. To eliminate respiratory variations, measurements from at least five consecutive cycles were averaged and index values were calculated using the regression equations given by Weissler and colleagues. Resting and exercise STI of patients with MVP were compared with a control group of 10 healthy male medical students of similar age. Neither patients nor control subjects were taking any drugs. Data were analyzed statistically by the t test for two means and are reported as mean ± standard error of the mean ($\bar{x}$ ± SEM).

Results

1. **Preejection period index (PEP_I).** In patients with mitral valve prolapse PEP in the *supine position* was 136.6 ± 3.4 msec. and 134.1 ± 4.0 msec. in the control group (not significant [NS]) (Fig. 1).

In the *upright position* PEP measured 153.5 ± 4.9 msec. in patients with MVP and 154.7 ± 4.6 msec. in controls (NS) (Fig. 1).

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Table I Clinical data of 14 patients with mitral valve prolapse

Patients	*Age*	*Sex*	*Symptoms*	*Resting ECG*	*Nonejection systolic clicks (No.)*	*Late systolic murmur*	*Chest x-ray*	*Echocardiogram (late systolic or holosystolic prolapse)*
K. B.	28	M	None	WNL	1	+	WNL	No detectable prolapse
B. F	25	M	None	LAHB*	1	+	WNL	+
S. R.	20	F	Atypical chest pain	WNL	1	+	WNL	+
B. M.	26	F	None	WNL	1	−	WNL	+
R. E.	28	F	None	WNL	1	+	WNL	+
C. R.	22	F	None	WNL	2	+	WNL	+
A. M.	36	F	None	WNL	1	+	WNL	+
D. M.	30	F	None	Diaphragmatic disturbance of repolarization	1	+	WNL	+
G. G.	27	F	None	WNL	1	+	WNL	+
A. P	23	M	None	WNL	1	+	WNL	+
B. B.	20	M	Atypical chest pain	WNL	1	+	WNL	+
S. A	29	F	None	WNL	1	+	WNL	+
K. R.	35	M	Atypical chest pain, palpitations	1 AV-block	0	+	WNL	+
S. R.	43	M	Atypical chest pain	WNL	1	+	WNL	+

*WNL = within normal limits, LAHB = left anterior hemiblock

Following *exercise* in the upright position PEP was 119.2 ± 3.6 msec. in patients with MVP and 116.3 ± 2.6 msec. in controls (NS) (Fig. 1)

2. Left ventricular ejection time index (LVET$_I$) In patients with mitral valve prolapse examined in the *supine position* LVET measured 420.4 ± 4.6 msec. and 409.8 ± 4.6 msec. in the control group (NS)

In the upright position LVET was 392.1 ± 5.0 msec. in patients with MVP compared with 388.4 ± 4.4 msec. in healthy controls (NS).

Following *exercise* LVET was 423.1 ± 5.8 msec. but 405.6 ± 3.9 msec. in our control group ($2\ p < 0.025$)

3. PEP/LVET ratio In patients with mitral valve prolapse PEP/LVET in the *supine position* was 0.354 ± 0.015 vs. 0.345 ± 0.018 in the control group (NS) (Fig. 1)

In the *upright position* PEP/LVET measured 0.442 ± 0.029 in patients with MVP and 0.443 ± 0.028 in controls (NS) (Fig. 1).

After *exercise* PEP/LVET was 0.303 ± 0.020 in patients with MVP compared with 0.335 ± 0.017 in the healthy subjects (NS) (Fig. 1).

There were no significant differences in blood pressure between the two groups at rest (in the supine and upright position) and after exercise.

Comments

There is general agreement that in the absence of cardioactive drugs, left bundle branch block, significant changes in preload and afterload and valvular heart disease, pre-ejection period and the ratio preejection period/left ventricular ejection time are good indicators of left ventricular function. In our study we found no evidence for impaired left ventricular function in patients with MVP as shown by a normal PEP and PEP/LVET ratio. This is in good agreement with the results of Scampardonis and associates, who found no hemodynamic and angiographic evidence of abnormal left ventricular function in most of their 87 cases. Change in posture or mild exercise revealed no significant difference in PEP and PEP/LVET between healthy controls and our patients. The slightly prolonged LVET in patients with MVP after exercise is not explained but does not indicate decreased myocardial contractility. The four patients with atypical chest pain had a slightly increased ratio PEP/LVET if compared with the asymptomatic patients. In view of their small number we would, however hesitate to draw any conclusions on myocardial function in this particular subgroup. It should also be emphasized that our observations were made in mildly symptomatic or asymp-

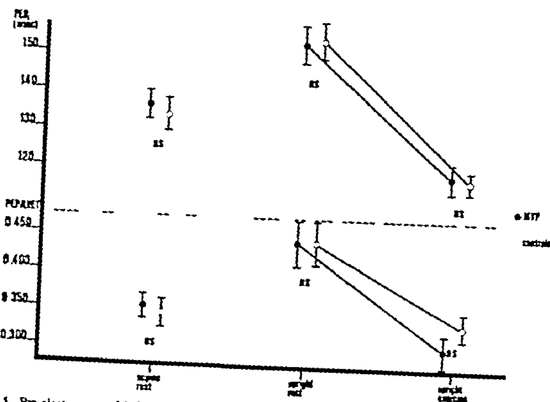


Fig. 1. Pre-ejection period index (PEP) and PEP/LVET ratio (x̄ ± SEM) in the supine and upright position before and following exercise in patients with mitral valve prolapse (MVP) and in healthy control subjects.

tomatic young patients and cannot be generalized to severe cases of MVP particularly with advanced age. Other investigators studied tients of a higher age group (mean 41 years) th symptomatic forms of MVP and found both emodynamic and angiographic evidence for ventricular dysfunction. Significant mitral regurgitation alone appears to be an insufficient explanation since only nine of their 28 patients exhibited mitral regurgitation of Grade II IV. Thus it may well be that impaired myocardial function in patients with MVP develops with increasing age.

We conclude that young patients with mild forms of mitral valve prolapse appear to have no significant left ventricular dysfunction. It remains to be established whether left ventricular function is impaired in certain subgroups of this disease (e.g., patients with atypical chest pain or with abnormal repolarization in the ECG).

Summary

To evaluate myocardial function in patients with documented mitral valve prolapse (MVP) 14 patients (six men and eight women with a mean age of 28 ± 6.8 years) were examined noninvasively. Systolic time intervals were recorded at rest (in the supine and upright position) and after bicycle ergometry (upright position) and were compared with 10 healthy control subjects of similar age. Tracings were coded with random numbers and were evaluated by two blinded investigators. Contractility indices such as preejection period index (PEP) and ratio preejection period/left ventricular ejection time (PEP/LVET) revealed no significant differences between patients and controls both at rest and after exercise. We conclude that young patients with MVP have no evidence for impaired myocardial function, provided there is no significant mitral incompetence or associated heart disease.

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The HQ time in congestive cardiomyopathies

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There are many reports in the literature on conduction disturbances in congestive cardiomyopathy but there are only few reports on His bundle recordings in this disease. To investigate the question whether there are distal conduction disturbances even in the absence of bundle branch block and whether there are associations with hemodynamic findings, we investigated His bundle recordings in 44 patients with congestive cardiomyopathy (COCM) and compared them with those of patients with ischemic cardiomyopathy (ICM) and similar ejection fractions.

ial and methods

Forty four patients with COCM were investi-ed. Patients on antiarrhythmic therapy were excluded. COCM was defined if two of the following criteria of abnormal left ventricular function (LVF) were present Increased left ventricular end-diastolic pressure (LVEDP) decreased ejection fraction (EF) (normal value in our laboratory 60 to 80 per cent) and presence of local or diffuse asynergy The volumes were calculated in single plane RAO projections. Regional wall motion was calculated by superimposing the end diastolic and end-systolic center of gravity and by turning parallel the long axes from the middle of the aortic valve to the apex. From the center of gravity the per cent systolic shortening was calculated in 20 degree steps starting from 40 degrees to 280 degrees. A normal contraction band (mean of systolic shortening ±1 standard deviation for each angle) was derived from 15 normals. Asynergy was defined if there was a deviation from the normal band in at least three angles.

Coronary artery disease valvular heart disease, mitral valve prolapse, and systemic hypertension were excluded. All patients underwent a His bundle study* during the right heart catheterization. Only the HQ time was measured because the majority of the patients received digitalis which influences the AH time and heart rate. The HQ time was measured from the onset of the His bundle deflection to the onset of the Q or first ventricular activation in the monitoring lead with a paper speed of 100 mm /sec. The intracardiac ECG from the bipolar electrode was filtered below 40 Hz and above 500 Hz. The normal limit in our lab is 35 to 55 msec. No atrial pacing studies were performed. In addition the LVEDP was measured and an LV angiogram and selective coronary angiogram was performed by the Judkins technique

In 21 patients with diffuse ICM (defined as diminished LV function similar to COCM but on the basis of severe triple vessel disease) the HQ time was studied as well.

Results

Congestive cardiomyopathy Among the patients studied, there were 32 males and 12 females. The mean age was 47 ± 10 years. Fig. 1 demonstrates the findings in the conventional ECG leads and the His bundle recordings. Twenty-seven per cent had a left bundle branch block, 5 per cent a bifascicular block, (right bundle branch block plus left axis deviation ≥ 60 degrees) 9 per cent a right bundle branch block,

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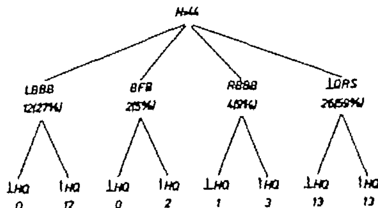


Fig. 1. The distribution of the conduction disturbances in 44 patients with congestive cardiomyopathy in the standard ECG and His bundle recordings. Abbreviations: *BFB* = bifascicular block, *LBBB* = left bundle branch block; *RBBB* = right bundle branch block; ⊥*HQ* = normal HQ time; ↕*HQ* = prolonged HQ time; ⊥*QRS* = normal QRS complex.

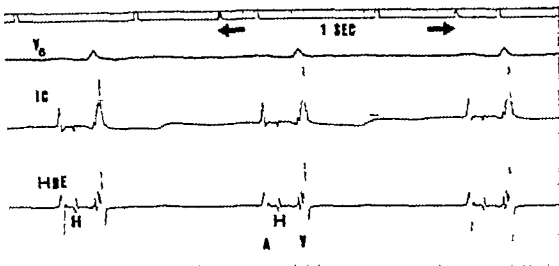


Fig. 2. His bundle recording of patient with normal QRS complex and HQ prolongation (patient No. 17 in Table II). Abbreviations: V = Lead V_6, *HBE* = His bundle recording; *IC* = nonfiltred intracardiac His bundle recording. Paper speed = 100 mm. per sec. The HQ time is 70 msec. and the width of the QRS complex is 70 msec.

and 59 per cent a normal QRS complex (QRS duration ≤ 0.1 sec.). Only one patient (patient No. 44 in Table I) with bundle branch block had a normal HQ time. Out of 26 patients with normal QRS complexes, 13 showed a prolonged HQ time (one example is given in Fig. 2, patient No. 17 in Table I) and 13 had a normal HQ time. Thus, out of 44 patients only 14 (32 per cent) had a normal HQ time. Fig. 3 shows an example of a patient with left bundle branch block and prolonged HQ time (patient No. 32 in Table I). The other results are summarized in Table I.

To investigate the relationship between the HQ time and ventricular function we compared the EF of three groups (Fig. 4). Firstly patients with normal QRS complexes and prolonged HQ time, secondly patients with left bundle branch block (all of them had a prolonged HQ time) and thirdly patients with normal QRS complexes and normal HQ time. In 36 patients out of this group technically satisfactory LV angiograms could be obtained and the EF could be calculated. In two patients the ejection fraction could not be calculated, but it was obvious that the ventricle did not contract normally and the LVEDP was elevated. Therefore these two patients were included. As the figure shows, the patients with a normal HQ time had a significantly better EF than patients with left bundle branch block and prolonged HQ time and patients with normal QRS complexes

Table I Patients with congestive cardiomyopathy (COCM) listed according to the standard ECG and His bundle recordings

	No.	*Age*	*Sex*	*EF*	*EDV*	*HQ*	*RH*
QRS⊥ HQ ≤ 55, N = 13)							
	1	62	F	68	81	50	SR
	2	47	M	50	87	50	SR
	3	38	M	48	80	50	SR
	4	47	M	—	—	50	SR
	5	57	M	43	106	50	SR
	6	38	M	61	98	55	SR
	7	37	M	51	74	55	SR
	8	57	M	63	117	50	SR
	9	48	M	—	—	50	SR
	10	48	M	47	204	50	SR
	11	23	M	29	96	40	SR
	12	38	M	40	115	50	SR
	13	54	F	36	102	55	SR
X̄		44.5		47.8	106.0		
SD		9 7		11.0	35.6		
QRS⊥(HQ ≥ 56, N = 13)							
	14	46	M	27	114	65	SR
	15	23	M	22	147	60	SR
	16	46	F	48	102	60	SR
	17	42	F	23	95	70	SR
	18	44	M	23	110	60	SR
	19	44	M	18	99	60	AF
	20	49	M	20	206	70	SR
	21	13	M	21	159	70	SR
	22	55	F	33	265	65	SR
	23	54	M	18	128	60	SR
	24	46	M	22	135	60	SR
	25	45	M	49	82	65	SR
	26	48	M	21	125	60	AF
X̄		42.9		26.5	135.9		
SD		11.6		11 0	60.4		

Abbreviations: EF = ejection fraction in per cent, RH = rhythm; HQ = HQ time in msec F = female; M = male; SR = sinus rhythm, AF = atrial fibrillation, BFB = bifascicular block, LBBB = left bundle branch block, RBBB = right bundle branch block; EDV = end-diastolic volume in ml/M. QRS⊥ = normal QRS

Table I Continued

	No.	*Age*	*Sex*	*EF*	*EDV*	*HQ*	*RH*
LBBB (HQ ≥ 56, N = 12)							
	27	64	F	42	126	60	SR
	28	47	M	34	88	70	SR
	29	55	M	36	74	95	SR
	30	66	F	37	79	60	SR
	31	49	M	27	161	120	SR
	32	56	F	19	122	80	SR
	33	40	M	26	216	80	SR
	34	58	M	28	157	70	SR
	35	38	F	44	108	60	SR
	36	51	F	35	116	60	SR
	37	47	M	26	181	60	SR
	38	56	F	33	64	60	SR
X̄		50.3		32.3	123.8		
SD		6.8		7.3	46.0		
BFB (HQ ≥ 56, N = 2)							
	39	46	M	—	—	70	SR
	40	60	M	37	110	70	SR
X̄ (LBBB + BFB)		50.7		32.6	122.5		
	SD	6.9		7.1	44.2		
RBBB (HQ ≥ 56, N = 3)							
	41	62	F	19	138	90	SR
	42	57	M	44	107	65	SR
	43	48	M	30	147	70	SR
RBBB (HQ ≥ 55, N = 1)							
	44	65	M	24	90	55	SR
X̄ (overall)		47.1		34.4	122.0		
SD		10.1		12.7	43.1		

and a prolonged HQ time (Student's t test) This indicates a close relationship between HQ time and ventricular function in patients with COCM. The end-diastolic volumes (normal range 90 ± 20 mL) in these groups were also compared (Table I) Although there was a tendency to higher end diastolic volumes in the groups with prolonged HQ time, the differences were not statistically significant.

Comparison with ischemic cardiomyopathy To compare the findings of the HQ prolongation 21 patients with severe diffuse ischemic cardiomyopathy were studied by His bundle electrocardiography (Table II). The ejection fraction was similar to those with COCM (27 1 ± 9.5 per cent as compared to 34.4 ± 12.7 per cent in COCM). The end-diastolic volume of the whole group was 124.6 ± 52.8 ml. as compared to 122.0 ± 43.1 in COCM. Because of the low incidence of HQ prolongation in ICM we could not compare the end-diastolic volume of subgroups statistically

It was found that only three out of these 21 patients with ICM had a prolonged HQ time as compared to 30 out of 44 patients with COCM. This difference is statistically significant ($p < 0.001$, chi-square test) If patients with normal QRS complexes were compared, 13 out of 26 patients with COCM had a prolonged HQ time while only two out of 15 patients in ischemic cardiomyopathy had a prolonged HQ time. This difference is also statistically significant ($p < 0.05$)

Discussion

The occurrence of bundle branch block in our patient group of COCM is quite similar to that

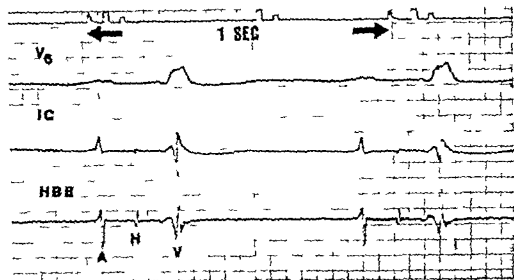


Fig. 3. A patient with left bundle branch block and prolonged HQ time (patient No. 33 in Table I). The HQ time is 80 msec. and the width of the QRS complex is 120 msec. For abbreviations see *Fig. 2*. Paper speed is 100 mm. per sec.

reported by others. Walmer and colleagues' found in 31 per cent a left bundle branch block, Hess and associates had similar findings' in 25 per cent and Kuhn and co-workers' saw it in 27 per cent. In contrast, right bundle branch block is a rather rare finding in COCM. None of our patients showed a total AV block. The lower incidence of total AV block in COCM is probably related to the poor prognosis of this disease.

The interesting finding is the high incidence of HQ prolongation in comparison to patients with ICM. Not only patients with bundle branch block had a high incidence of HQ prolongation in COCM, but also patients with normal QRS complexes. The differences were statistically significant. Walmer and colleagues' found in two out of 12 patients with normal QRS complexes an HQ prolongation. This lower incidence as compared to our findings might be explained by different stages of the disease in this patient group. Hemodynamic data in this paper were not given; thus, we were unable to compare the findings.

There are three possibilities of HQ prolongation with a normal width of QRS complexes. Firstly intra-Hisian block, secondly cardiac enlargement[1-] thirdly diffuse and equal prolongation of conduction in the left and right bundle branch.

In our opinion this predominance of HQ prolongation in COCM can not be explained by intra-Hisian block. An intra-Hisian block would suggest a localized lesion in the His bundle itself. It could not be explained by a predominance of localized lesions in the His bundle in COCM as compared to ICM. We rather would expect the same incidence or even a higher incidence of a focal lesion in ICM. A localized lesion in the His bundle could also not explain the negative correlation with the ejection fraction. In our patient population only 32 per cent of patients with COCM had a normal HQ time, while in ICM we found in 85 per cent a normal HQ time. In COCM only one patient with bundle branch block had a normal HQ time while only one out of six patients with bundle branch block and ICM had a prolonged HQ time. Ventricular dilatation as etiologic factor can also be excluded because of the similar end-diastolic volumes between the two different patient populations. Because of the low incidence of HQ prolongation in ICM, subgroups could not be compared but the mean values of both groups showed no significant differences. Although there was a tendency to left ventricular enlargement in patients with HQ prolongation within the group of COCM, the differences were not significant. We have to point out that two out of the patients with ICM and normal QRS complexes and prolonged HQ time showed an extremely high EDV (patients No. 14 and 16 in Table II). Thus, in certain cases with very high left ventricular end-diastolic volumes HQ prolongation might be caused by ventricular enlargement. However our data (Tables I and II) do not support such a mechanism of HQ prolongation in COCM.

The most attractive hypothesis seems to be the

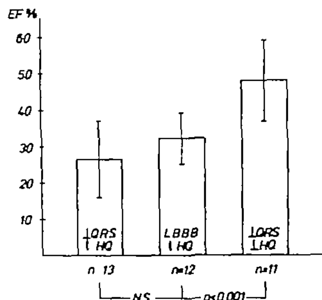


Fig. 4 The figure shows the comparison of the jection fractions of patients with normal QRS complex and prolonged HQ time (*on the left*), left bundle branch block and prolonged HQ time (*in the middle*), and normal QRS complexes and normal HQ time (*on the right*). There is no difference of EF between patients with normal QRS complex and prolonged HQ time and left bundle branch block and prolonged HQ time, but there is highly significant difference between patients with prolonged HQ time and the patients with normal QRS complexes and normal HQ time. For abbreviations see *Fig. 1*

equal involvement of both bundle branches by the same disease in COCM. If the disease is not advanced the bundle branches conduct normally With progression of the disease and lowering of the EF the bundle branches get involved and HQ time prolongs. These findings indicate that COCM is a diffuse disease of the myocardium including the conduction system. If there is an equal involvement of the right and the left bundle branch the HQ time prolongs without resulting in bundle branch block. If one side is involved to a higher degree bundle branch block develops which is more common on the left than on the right side because of a higher work load of the left ventricle.

Only two patients do not fit into this concept. Patient No 11 (Table I) who has a low EF and a normal HQ time, and patient No 44 who has right bundle branch block, a normal ejection fraction, and normal HQ time Since the etiology of COCM is not known we could imagine that different underlying mechanisms might influence the bundle branches in a different way For instance, myocarditis, which is a difficult differential diagnosis to cardiomyopathy might be the

Table II Patients with ischemic cardiomyopathy (ICM) listed according to the standard ECG and His bundle recordings

		Age	*Sex*	*EF*	*EDV*	*HQ*	*RH*
QRS⊥(HQ ≦ 55, N = 13)							
	1	50	M	15	142	46	SR
	2	39	M	36	107	55	SR
	3	35	M	32	69	50	SR
	4	63	M	30	103	40	SR
	5	44	M	43	100	40	SR
	6	69	M	18	183	55	SR
	7	57	M	21	134	50	SR
	8	66	M	20	122	50	SR
	9	50	M	47	70	40	SR
	10	64	M	22	143	35	SR
	11	57	M	27	78	50	SR
	12	66	M	12	126	40	SR
	13	66	M	33	118	55	AF
X		61.0		27.3	118.9		
SD		7.4		10.6	26.5		
QRS⊥(HQ ≧ 56, N = 2)							
	14	63	M	33	264	70	SR
	15	55	M	25	261	66	SR
BFB (HQ ≦ 55, N = 2)							
	16	59	M	16	105	55	SR
	17	38	M	28	126	55	SR
LBBB (HQ ≦ 55, N = 3)							
	18	62	M	35	76	55	SR
	19	66	M	23	107	40	SR
	20	58	M	30	102	50	SR
LBBB (HQ ≧ 56, N = 1)							
	21	43	M	40	67	60	SR
X (BFB + LBBB)				28.7	97.5		
SD				8.5	22.3		
X (*overall*)		61.7		27.1	124.6		
SD		7.6		9.5	42.6		

Abbreviations: same as in Table I.

underlying mechanism in these two cases, explaining that the conduction system is not involved in the same way as in the patients with COCM

In ICM HQ prolongation is a rare finding. This disease does not diffusely involve the whole myocardium and the specific conduction system but is rather patchy It was also shown that the subendocardial Purkinje network is spared or recovers within the ischemic areas in ischemic heart disease. Thus, there are areas of the conduction system which always conduct to the ventricles normally If there is HQ prolongation with normal QRS complexes in ICM we expect intra Hisian block.

The close relationship between HQ time and EF *indicates that patients with COCM* and prolonged HQ time have a poor prognosis. This confirms the electrophysiologic findings of Denes and co-workers[10] and Dhingra and associates who showed that patients with bundle branch block and HQ prolongation had a poor long term prognosis—not because of the development of *total AV block, and sudden death, respectively* but because of heart failure. Most of these patients probably had COCM. (The diagnosis was not confirmed by selective coronary arteriograms)

We believe that HQ prolongation is a characteristic feature of advanced COCM Its value in *the differential diagnosis of other forms of* myocardial disease requires further evaluation.

Summary

1. In 41 per cent of patients with COCM there was a bundle branch block. All but one of these 18 patients showed a prolonged HQ time, indicating *that the whole conduction system* in these cases is involved and that there is just a predominance of one side.

2. Fifty nine per cent had a normal QRS complex and 50 per cent of these patients showed a prolonged HQ time. It must be assumed that in these cases the whole conduction system is diffusely involved to the same degree. This results in a pure HQ prolongation and not in bundle branch block.

3. Patients with ICM showed significantly less often an HQ prolongation, indicating that the conduction system in these cases is not diffusely involved.

4. The significant negative correlation between HQ time and EF indicates that the progression of the myocardial disease is concomitant with the progression of the conduction disturbances, which *can be either diffuse in both branches, leading to a* pure HQ prolongation, or be predominant in one of the bundles, leading to a bundle branch block with an HQ prolongation.

5 There are no significant differences of the end-diastolic volumes within the group of COCM and between patients with COCM and ICM. Thus, ventricular enlargement, and myocardial dilatation, respectively are not the cause of HQ prolongation.

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Postoperative arrhythmias after coronary artery and cardiac valvular surgery detected by long term electrocardiographic monitoring

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Coronary artery bypass graft surgery has become an increasingly frequent therapeutic modality employed in the management of coronary artery disease. Technical advances and improved perioperative care have reduced the operative mortality of coronary artery bypass graft surgery with the result that more attention is now focused on techniques to decrease morbid complications. Similar advances have occurred in valvular surgery.

The present prospective study was designed to better quantify the contribution of arrhythmias to the morbidity of coronary artery bypass graft surgery. The technique of "ambulatory" long term electrocardiographic recording was applied to extend routine methods of perioperative arrhythmia detection to evaluate the incidence and characteristics of arrhythmias after coronary artery bypass graft surgery, their clinical significance, and the extent that long term electrocardiographic recordings supplement routine monitoring in detecting arrhythmias. In addition, a smaller number of patients undergoing cardiac valve replacement was also studied to determine the relationship of arrhythmias to the underlying cardiac disease.

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Methods

The study included 70 patients of which 55 were male with a mean age of 56 ± 10 years (SD) (range: 27 to 81 years). These patients were referred to one cardiothoracic surgeon (H. M.) during a two month period. Coronary artery bypass graft surgery was performed in 50 patients, 41 were male; mean age was 54 ± 9 years (SD). Seventeen patients underwent cardiac valve replacement, 13 aortic, three mitral and one aortic, mitral and tricuspid. Twelve of these patients were male. The mean age was 60 ± 12 years (SD). Three patients underwent both coronary artery bypass graft surgery and aortic valve replacement; two were male; mean age was 60 ± 5 years (SD). Of the patients undergoing coronary artery bypass surgery 37 had propranolol prescribed preoperatively, five had propranolol plus either quinidine or procainamide, and one only had quinidine. Three patients undergoing valvular surgery were taking either quinidine or procainamide preoperatively and one was taking propranolol. Preoperatively propranolol dosage was tapered to 50 per cent of baseline during the 24 hours before coronary artery bypass graft surgery.

All surgery was performed at the Hospital of the University of Pennsylvania and patients were selected prospectively and consecutively for this study on the basis of availability of long term electrocardiographic recorders at the time of admission. Anesthetic and surgical techniques were constant throughout. During coronary artery bypass graft surgery, no patients required ventricular vents, and no patients had previous chest surgery. All patients had 24 hour long-term

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electrocardiographic monitoring with a two-channel (simultaneous Leads V and V) Avionics 445 recorder the day before surgery and again postoperatively on the first and fifth days after discharge from the Surgical Intensive Care Unit (SICU) All but two patients were discharged from the SICU on the second or third postoperative day Long-term electrocardiographic recordings were analyzed with an Avionics 660A scanner using a research service with an error rate in ectopic frequency analysis determined to be 7 per cent in comparison to real time analysis. Arrhythmias were confirmed in addition by two cardiologists. All patients were seen daily by both a cardiothoracic surgeon and cardiologist and were carefully evaluated for the presence of arrhythmias, as well as for the development of specific postoperative complications which included excessive bleeding, pericarditis, new postoperative Q waves on the electrocardiogram, recurrent angina, complete heart block, congestive heart failure, low cardiac output, thromboembolism, cardiac tamponade or infection. Continuous electrocardiographic evaluation using standard Intensive Care Unit monitoring was performed routinely in the SICU Routinely patients had 12 lead ECGs before surgery daily in the SICU and every other day thereafter until discharge from the hospital. Two of the 17 patients undergoing valvular surgery were not available for long term electrocardiographic monitoring postoperatively and were excluded from further analysis. One (aortic) died intraoperatively and the other (aortic, mitral and tricuspid) died while still in the Surgical Intensive Care Unit with persistent hypotension. Arrhythmias were not considered to have contributed to the death of either patient. No antiarrhythmic therapy was prescribed prophylactically in the postoperative period.

The following were defined as significant arrhythmias:

Atrial

1 Atrial fibrillation or flutter whether paroxysmal or sustained

2. Reentrant or automatic paroxysmal supraventricular tachycardia (SVT)

3. Frequent atrial premature depolarizations (APDs) (≥ 5 per minute)

Ventricular

1. Unifocal ventricular premature depolarizations (VPDs), ≥ 30 per hour

2. Ventricular couplets

Table I Arrhythmias in patients undergoing coronary artery bypass graft surgery

Before OR§	*N*	*Postoperative period* APDs	AF	A flutter	SVT	None
Atrial arrhythmias						
APDs ≥ 5/min.	2	—	1	—	—	1
SVT	3	—	—	—	1	2
None	45	3	7†	3‡	4	28
	50					31

Before OR	*N*	*Multiform Ventricular* VPDs ≥ 30/hr	VPDs	Couplets	VT	None
Ventricular arrhythmias						
VPDs ≥ 30/hr.	4	—	—	1	2‖	1
Multiform & couplets	1	—	1¶	—	—	—
None	45	5‖	1	6	2	31
	50					32

Abbreviations: APDs = atrial premature depolarizations, AF = atrial fibrillation, A flutter = atrial flutter; SVT = supraventricular tachycardia; VPDs = ventricular premature depolarizations; VT = ventricular tachycardia, OR = operation; N = number of patients.

Also had atrial flutter and SVT

†One also had atrial flutter

‡One also had SVT

§No patients had atrial fibrillation or flutter before OR.

‖Two also had ventricular couplets.

¶ Also had VPDs ≥ 30/hr. and ventricular couplets.

#No patient had VT before OR.

3. Ventricular tachycardia (≥ 3 consecutive VPDs)

4. Multiform VPDs.

A patient was considered to have a new atrial arrhythmia if significant atrial arrhythmias occurred postoperatively and none had occurred preoperatively The presence of a different atrial arrhythmia postoperatively in a patient with a preoperative atrial arrhythmia was not considered new" Similarly new ventricular arrhythmias were defined by the occurrence of a significant ventricular arrhythmia postoperatively if none had occurred preoperatively

Results

Patients undergoing CABG surgery Atrial and/or ventricular arrhythmias were recognized postoperatively in 32 of 50 patients (64 per cent) 14 patients had atrial arrhythmias, 13 had ventricular arrhythmias, and five patients had

Table II Preoperative and postoperative arrhythmia occurrence in patients undergoing coronary artery bypass graft surgery

No. of vessels bypassed	N	Arrhythmias: Ventricular	Atrial	Ventricular & atrial	No arrhythmias	
1	5	1	1	0	3	pre op
		0	2	1	2	post op
2	14	2	2	0	10	pre op
		5	3	0	6	post op
3	24	2	2	0	20	pre op
		5	6	3	10	post op
4	7	0	0	0	7	pre op
		2	2	2	1	post op
	50	5	5	0	40	pre op
		12	13	6	19	post op

Abbreviations: Preop = arrhythmias detected preoperatively; Post op = arrhythmias detected postoperatively; N = number of patients.

both atrial and ventricular arrhythmias. The most common arrhythmias were atrial fibrillation (eight patients) and ventricular couplets (12 patients) Twenty-six of these 32 patients had new postoperative arrhythmias, 12 atrial nine ventricular and five both atrial and ventricular arrhythmias.

Atrial arrhythmias. Nineteen of 50 patients (38 per cent) had postoperative atrial arrhythmias (Table I) Seventeen of these 19 had new atrial arrhythmias and two patients had persistence of preoperative atrial arrhythmias. Postoperative arrhythmias were detected exclusively by long term ECG monitoring in ten of all 19 patients with postoperative atrial arrhythmias (53 per cent) and in eight of the 17 patients with new atrial arrhythmias (47 per cent) Only three of the 19 patients (16 per cent) were on antiarrhythmic therapy before long term electrocardiographic recordings were taken. Of the eight patients with new atrial arrhythmias detected only by long term monitoring, two patients had their arrhythmias noted on both postoperative long term recordings and two patients on only the second postoperative 24-hour electrocardiographic recording.

Ventricular arrhythmias. Eighteen of 50 patients (36 per cent) had postoperative ventricular arrhythmias (Table I) These included 14 patients with new postoperative arrhythmias plus four patients with persistence of arrhythmias noted preoperatively Postoperative arrhythmias were detected exclusively by long term ECG monitoring in 14 of all 18 patients with postoperative ventricular arrhythmias and in 13 of 14 patients with new ventricular arrhythmias. Of the four patients with ventricular tachycardia, three were not detected by standard monitoring and were noted only by long term electrocardiography Of all 18 patients with postoperative ventricular arrhythmias, only six were on antiarrhythmic therapy before the results of 24-hour electrocardiographic monitoring were available. These six patients were all prescribed antiarrhythmic therapy (quinidine or procainamide) for clinically recognized arrhythmias. Of the 13 patients with new arrhythmias detected only by long term electrocardiography two had these recorded on both postoperative 24-hour recordings and five on only the last 24 hour ambulatory" electrocardiographic recording.

The extent of revascularization is compared in Table II with the occurrence of preoperative and postoperative atrial and ventricular arrhythmias. The occurrence of arrhythmias preoperatively was infrequent and did not correlate with the number of vessels subsequently bypassed. Arrhythmias were common postoperatively in all groups but a trend was noted towards an increased frequency of arrhythmias (especially atrial fibrillation and ventricular tachycardia) in patients with more extensive revascularization. Three of the four patients with ventricular tachycardia and five of the six with atrial fibrillation had extensive revascularization (three or four coronary grafts) Ejection fractions, left ventricular end-diastolic pressures, and the presence of segmental wall abnormalities did not correlate statistically with the occurrence of either preoperative or postoperative arrhythmias. No in-hospital deaths occurred in the 50 patients undergoing coronary artery bypass graft surgery

Patients undergoing valvular surgery Postoperative arrhythmias were detected in 12 of 15 patients (80 per cent) after valve surgery nine had atrial and 3 had ventricular arrhythmias (Table III) The most common arrhythmia was atrial fibrillation (seven patients) The 12 patients with postoperative arrhythmias included

Table III Arrhythmias in patients undergoing valvular surgery

Before OR‡	*N*	*Postoperative period* — *AF*	*A flutter*	*SVT*	*APDs ≥ 5/min.*	*None*
Atrial arrhythmias						
APDs ≥ 5/min.	1	–	–	–	1	–
AF	4	4	–	–	–	–
SVT	1	–	–	–	–	1
None	9	2	–	1†	1	5
	15					6

Before OR§	*N*	*Postoperative period‖* — *VPDs ≥ 30/hr*	*Multiform VPDs*	*None*
Ventricular arrhythmias				
VPDs ≥ 30/hr.	1	–	–	1
Couplets	1	–	1	–
None	13	2	–	11
	15			12

Abbreviations. N = number of patients, AF = atrial fibrillation, A flutter = atrial flutter; SVT = supraventricular tachycardia, APDs = atrial premature depolarizations; VPDs = ventricular premature depolarizations; OR = operation

*Two also had atrial flutter.

†Also had atrial fibrillation.

‡No patients had atrial flutter before OR.

§No patients had multiform VPDs or VT before OR.

‖No patient had ventricular tachycardia or couplets postoperatively

Table IV Postoperative arrhythmia occurrence in patients with morbid complications

Morbidity	*N*	*CABG patients** — *No. with arrhythmias*	*None*	*N*	*Valve patients†* — *No. with arrhythmias*	*None*
Low cardiac output	1	1V		3	1A	2
Congestive failure	3	1V 1A + V	1	1	1CHB	
Tamponade	4	1A + V 1A 1V	1	0		
Persistent pericarditis	6	2A 2V	2	0		
Pneumonia	1	1V		1	1A	
New Q waves (ECG)	3	1A 1V	1	0		
Recurrent angina	1		1	0		
Thromboembolism	0			1	1A	
Wound (inflammation or drainage)	3	1A + V	2	0		
Hydro/Pneumothorax	3	1A 1A + V	1	1	1A	
Excessive bleeding	1	1A		0		

Abbreviations. A = atrial, V = ventricular; CHB = complete heart block, CABG = coronary artery bypass graft; N = number of patients.

*Sixteen patients had a total of 26 morbid complications.

†Five patients had seven morbid complications.

six (four atrial, two ventricular) with new postoperative arrhythmias, and three of these six were detected only by long term electrocardiographic monitoring. One patient with atrial fibrillation preoperatively also had new ventricular arrhythmias postoperatively. Seven of 15 patients had arrhythmias preoperatively (five atrial, one ventricular one both). Atrial fibrillation was the most common preoperative arrhythmia and persisted in all four cases postoperatively.

Atrial arrhythmias. Nine of 15 patients (60 per cent) had postoperative atrial arrhythmias. Four of these nine patients (all undergoing aortic valve replacement) had new postoperative arrhythmias. Five of six patients with preoperative atrial arrhythmias also had atrial arrhythmias postoperatively. Two of the nine patients with postoperative arrhythmias had these detected only by long term electrocardiographic monitoring and neither was on antiarrhythmic therapy before 24-hour electrocardiographic recordings were taken.

Ventricular arrhythmias. Three of 15 patients (20 per cent) had postoperative ventricular arrhythmias. In two patients, new ventricular arrhythmias appeared and, in one patient, preoperative ventricular arrhythmias persisted. These arrhythmias were noted only by 24-hour electrocardiographic monitoring in two of the three patients. Neither was on antiarrhythmic therapy before 24-hour electrocardiographic recordings were taken. No patient had ventricular tachycardia or ventricular fibrillation.

Combined valvular and CABG surgery. Three patients underwent combined aortic valve replacement and CABG surgery. One patient had preoperative arrhythmias recorded (supraventricular tachycardia and ventricular couplets) and these persisted postoperatively. Two patients had new postoperative arrhythmias, one had supra

ventricular tachycardia and the other had paroxysmal ventricular tachycardia.

Morbidity Although arrhythmias were observed commonly in association with both major and minor complications, there was no consistent relationship between their occurrence and the presence of these complications (Table IV). In addition, there were no data to indicate that arrhythmias further complicated the postoperative course of patients after either CABG or valvular surgery No patients had ventricular fibrillation four CABG patients had ventricular tachycardia and only one of these four had an otherwise complicated course (cardiac tamponade)

There was also no correlation observed between the occurrence of either atrial or ventricular arrhythmias postoperatively and either excessive chest tube drainage or prolonged duration of hospital stay

Two patients had junctional rhythms occurring after valvular surgery one of the two had persistent complete heart block and required a permanent pacemaker

Of the three patients undergoing combined aortic valve replacement and CABG surgery one had minor pulmonary complications prolonging hospitalization the other two had uneventful postoperative courses.

Arrhythmias were not considered to contribute to the mortality in any patient in this series.

Discussion

High incidence of new postoperative arrhythmias The use of repeated 24-hour long term electrocardiographic recordings to supplement intensive care unit monitoring routine 12 lead ECGs, and clinical follow up in the present study has revealed an unexpectedly high incidence of new arrhythmias after cardiac surgery [11]. Atrial arrhythmias were common preoperatively in patients with valvular heart disease and occurred frequently postoperatively after both valvular and CABG surgery Ventricular arrhythmias were uncommon preoperatively among either valve or CABG patients but occurred frequently after CABG surgery

Valvular surgery Previous studies reported that as many as 74 per cent of patients undergoing cardiac valve replacement had postoperative arrhythmias recognized during intensive care unit monitoring and with routine in hospital follow up ECGs atrial fibrillation was most common, and ventricular arrhythmias occurred infrequently [11]. Their high prevalence of reported arrhythmias," however also included patients with new conduction disturbances (32 per cent) as well as those with atrial fibrillation that was present preoperatively (36 per cent). Thus, the incidence of new postoperative arrhythmias, although not specifically determined in these studies, was apparently less than 20 per cent.

In our group of 15 patients undergoing valvular surgery 12 (83 per cent) had postoperative arrhythmias, the most common of which was atrial fibrillation. Six patients (40 per cent) had new postoperative arrhythmias (four atrial, two ventricular) The incidence of new postoperative arrhythmias in the present study was higher than previously reported. This can be directly attributed to an increase in arrhythmia detection due to the use of long term electrocardiographic monitoring. Our small number of patients, however precluded more detailed analysis of those undergoing valve replacement.

Coronary artery bypass graft surgery Previous studies have also evaluated the general incidence of arrhythmias after coronary artery bypass graft surgery In one series, 29 of 75 patients (39 per cent) had arrhythmias observed. These patients were not evaluated for arrhythmia frequency preoperatively however and the incidence of new arrhythmias is, therefore, not known. In our series, 32 of 50 patients (64 per cent) undergoing coronary artery bypass graft surgery had postoperative arrhythmias, and 26 (52 per cent) had new postoperative arrhythmias. This increased incidence of arrhythmias can be attributed again to enhanced detection because of the use of long-term ECG monitoring.

Arrhythmia detection Sixteen of 26 patients with new arrhythmias recorded after coronary artery bypass graft surgery had these arrhythmias detected only by 24-hour long term electrocardiographic monitoring. Four of 12 patients with arrhythmias after cardiac valve replacement and three of the six patients with new postoperative arrhythmias had these detected only on 24-hour electrocardiographic monitoring. It was also apparent from our data that seven of the 26 patients with new arrhythmias after coronary artery bypass graft surgery had their arrhythmias detected only on the second postoperative long term recording. Similarly two of six patients with

new arrhythmias after valve replacement had their arrhythmia recorded only on the second postoperative 24-hour electrocardiographic recording. This suggests the need for continued electrocardiographic follow up in selected patients.

Clinical significance More extended, in hospital monitoring would probably have revealed an even higher incidence of postoperative arrhythmias. Although these arrhythmias occurred so frequently their occurrence did not necessarily contribute significantly to other complications in the immediate postoperative period. Therefore, a decision to treat these will need to continue on an individual basis. Further follow up may determine whether these arrhythmias contribute to sudden death or to other complications after discharge.

In our clinical experience, paroxysmal supraventricular tachyarrhythmias were not well tolerated after either valve replacement or CABG surgery. Hemodynamically this was not surprising. However in some patients these arrhythmias produced no symptoms and would not have been detected without long term electrocardiographic recordings. Other patients reported shortness of breath or chest discomfort related to either the inciting cause or secondary to their arrhythmias. These symptoms often subsided without specific therapy.

Atrial arrhythmias occurred frequently before operation in patients with valvular heart disease. Presumably these were caused by left atrial dilatation and hypertrophy as well as by the residua of rheumatic myocarditis. New atrial arrhythmias appeared often postoperatively however after both valvular and CABG surgery. Their occurrence probably reflected the sequelae of cardiac surgery: mediastinal and pericardial inflammation, atelectasis, minor pulmonary complications, thromboembolism, atrial trauma (including atriotomy and vents), and atrial distention.

Ventricular arrhythmias were noted relatively infrequently before either valve replacement or coronary artery bypass graft surgery however 43 of 50 patients in the coronary artery bypass graft group were taking either propranolol or other antiarrhythmic therapy preoperatively. Ventricular arrhythmias were detected more frequently after coronary artery bypass graft surgery. In contrast to valvular surgery after coronary artery bypass graft surgery ventricular arrhythmias (38 per cent of patients) occurred almost as often as atrial arrhythmias (38 per cent). The occurrence of postoperative ventricular arrhythmias did not correlate, however with preoperative measurements of left ventricular function such as ejection fraction, left ventricular end diastolic pressure, the presence of segmental wall dyskinesis, or the presence of new postoperative Q-waves. Intraoperative non transmural infarctions were not excluded by our diagnostic methods, however. Ventricular arrhythmias persisted postoperatively in patients with preoperative ventricular arrhythmias in the majority of cases. In addition, a trend was observed toward an increased frequency of arrhythmias in those patients with more extensive revascularization.

It is not clear why ventricular arrhythmias occurred more frequently after coronary artery bypass graft surgery than after valvular surgery. Presumably these were related to underlying ischemia. Nuclear imaging and other techniques may shed light on whether these arrhythmias can be attributed to reperfusion of reversibly ischemic myocardium or rather to the residual changes of chronic ischemia, plus the effects of discontinuation of preoperative medications including propranolol. In general, however ventricular arrhythmias did not further complicate the postoperative management of patients with either coronary artery bypass graft surgery or cardiac valve replacement in this series.

Thus, the use of extended "ambulatory" electrocardiographic recordings to supplement routine postoperative monitoring has revealed a higher incidence of arrhythmias after cardiac surgery than previously suspected. Remarkably 52 per cent of coronary artery bypass graft patients and 40 per cent of valve patients have new atrial or ventricular arrhythmias in the first postoperative week. Atrial arrhythmias were frequent sequelae of both valvular and coronary artery bypass graft surgery whereas ventricular arrhythmias occurred more commonly after coronary artery bypass graft surgery.

Summary

Twenty four hour long term electrocardiographic recordings were used to supplement routine perioperative monitoring to determine the frequency and significance of arrhythmias occurring after coronary artery bypass graft

surgery and cardiac valve replacement. Patients underwent ambulatory" electrocardiographic monitoring for 24 hours before surgery and on the first and fifth days after discharge from intensive care.

New arrhythmias occurred in 26 of 50 patients (52 per cent) after coronary artery bypass graft surgery and in six of 15 patients (40 per cent) after valve replacement. This high frequency of arrhythmia detection was directly attributable to the use of long term electrocardiography New atrial arrhythmias were common after both valvular and coronary artery bypass graft surgery (44 per cent and 38 per cent of patients, respectively). Ventricular arrhythmias were uncommon preoperatively in both groups but occurred frequently after coronary artery bypass graft surgery (36 per cent). Arrhythmias contributed to morbidity but not to mortality in this series.

These results suggest that new atrial arrhythmias occurring after coronary artery bypass graft or valvular surgery may be related more to the immediate intrathoracic sequelae of surgery than to a specific underlying cardiac lesion in contrast to ventricular arrhythmias which may be more specific for patients with ischemia. Long term electrocardiographic recording is a useful technique to supplement routine methods of perioperative electrocardiographic monitoring.

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Evidence in favor of the vasospastic cause of coronary artery thrombosis

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There is growing evidence that acute myocardial infarction is associated with, and possibly due to coronary artery spasm.[1-3] This spasm, since it can occur in arteriosclerotic segments,[4-] and since it causes both physical and flow changes in the affected artery might also result in coronary artery thrombosis. The well-described microscopic changes in thrombosed coronary arteries might best be explained by a violent vascular constriction, and thus provide further support for the occurrence of vasospasm in acute myocardial infarction.

Epicardial spasm, intimal tears and plaque rupture and coronary artery thrombosis

Intimal tears, erosions, and fissures, only sometimes associated with plaque rupture and expulsion of grumous material, have been related to coronary thrombosis by a number of observers.[-21] They often are ascribed to ischemic ulcerations,[17-20] have been found in as high as 90 to 100 per cent of thrombosis,[14-20] and were absent in controls.[14]

While intimal tears and plaque rupture ordinarily are not related to coronary artery spasm, in 1934 Leary[22] proposed that plaque rupture was due to this phenomenon. He reported three cases of sudden cardiac death which had overriding psychic components and suggested that the only reasonable explanation was widespread hyper*sensitivity of the nervous system*" which caused "contraction of the coronary arteries under nervous control."

The spastic origin of intimal tears and plaque rupture is attractive to this observer It is likely that compressive forces of spasm could rupture the intima, and with soft plaques, extrude atheromatous material into the lumen. The occasionally observed admixture of plaque material with the thrombus[13, 6-21] appears to be in favor of a spastic origin of plaque rupture. Severe spasm would not only extrude plaque material into the lumen, it would also contain the plaque material so that it would remain *in situ* and be available for incorporation into the thrombus. With plaque rupture due to other causes, it is likely that fragments of exposed plaque material would be washed downstream, and would be unavailable for mixing into the thrombus at the site of the plaque rupture.

It has been postulated that intimal tears and plaque ruptures in arteriosclerotic plaques are due to application of physical forces. Chapman[16] implicated a "vector of disruptive force (which) proceeded from within the wall toward the lumen and Constantinides concluded that the sudden explosions of pressure within these arteriosclerotic arteries cracked their rigid wall." Horie and colleagues suggested that plaque rupture is due to increased intra-plaque pressure, because of infiltration through injured endothelium into the plaque. Of potential causes of mechanical stresses on plaques, spasm seems the most likely

Epicardial spasm and coronary artery hemorrhage

The occurrence of hemorrhage into coronary arteriosclerotic plaques[19, 20, 22-24] might offer mi

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nor evidence in favor of spasm. A violent seizure of the vessel, capable of disrupting the intima, probably also would cause plaque hemorrhage. Chapman also thought that the force (nonspastic) which caused plaque rupture could result in intimal hemorrhage. Plaques are vascularized, and these vessels are poorly supported in soft plaques and would be vulnerable to the torsional forces of spasm. However only hemorrhages which are unassociated with intimal rupture can be used as indirect evidence for spasm, as once the intima is torn there is open communication between plaque and lumen. Although intimal hemorrhages now usually are ascribed to intimal tears, in studies utilizing serial sections, hemorrhages have been found in the absence of intimal disruptions. Hemorrhages can occur with and without thrombosis, occasionally may be large enough to cause luminal obstruction, and have been considered as a primary cause of thrombosis.

The failure to observe plaque rupture and hemorrhage in all cases of coronary thrombosis should not negate a spastic cause of thrombosis. The incidence of these changes is disputed, and studies utilizing serial sections are more likely to demonstrate small lesions. Also it is reasonable that spastic contracture would not necessarily cause physical changes in the vessel. Extensive plaque rupture and evacuation of contents implies a soft plaque filled with grumous material; a fibrous intimal plaque and especially a normal vascular segment would be less likely to tear and hemorrhage.

2. Intramyocardial injury-spasm, coronary artery stasis or no-reflow, and coronary thrombosis

We have also suggested that spasm might be involved in coronary thrombosis, and arrived at this conclusion by an approach different than Leary's. We proposed that a reasonable explanation for thrombosis would be a marked reduction in blood flow in the artery subtended by the infarct, because of changes within the infarcted muscle. Such impaired flow was demonstrated experimentally and because it was reversed by vasodilation and involved a [illegible] nuation of the hyperemic response it was attributed to ongoing spasm of intramyocardial arteries. This apparent spasm was ascribed to an acute injury reaction caused by the fresh necrosis of infarction. Also it appears equivalent to the post-ligation coronary artery spasm as described by Grayson and Lapin.[37] At the present time, reduced flow during infarction generally is designated as the no-reflow phenomenon,[38] and there is no general agreement as to its cause.

Proposed mechanisms for coronary thrombosis

Coronary artery spasm of epicardial and intramyocardial origin, is considered to initiate both infarcts and coronary thrombosis. Thrombosis follows intimal tearing and plaque rupture of epicardial arteries, and the coronary artery stasis which accompanies spasm of both epicardial and mural arteries. The stasis augments the thrombogenic effect of intimal disruption. The initial episode of spasm probably produces complete epicardial obstruction, and there is angiographic evidence for this. Even after relaxation of the epicardial component of the original paroxysm of spasm, intramyocardial spasm would continue due to fresh injury spasm from acute muscle necrosis, causing the no-reflow phenomenon. In the minority of cases where there is extensive intraluminal rupture of plaque material, thrombosis probably occurs fairly rapidly. With small or microscopic intimal tears, or in the absence of tearing, continuing stasis probably plays the dominant role in thrombus formation. The importance of stasis occurring over a period of time is suggested by the higher incidence of thrombosis in individuals dying later in the course of infarction.

It is reasonable that a milder episode of spasm would be associated with a lower frequency of thrombosis. Mild spasm would tend to rupture plaques less frequently and any intimal tear would tend to be smaller. Also, an attack of mild spasm probably would resolve reasonably promptly permitting necrosis to be limited to the subendocardium. These concepts are in keeping with the lesser incidence of thrombosis in subendocardial infarction. Conversely severe spasm would tend to rupture plaques, and the resultant thrombus, because of its usually permanent and complete vascular obstruction, would enlarge infarcts. Consistent with this, large transmural infarcts often are associated with thrombosis. Occasionally large infarcts are not complicated by thrombosis, and this might be explained by delayed resolution of a severe episode of spasm, where the protracted ischemia would also result

in a larger infarct. Or there could be extension of intramyocardial spasm.

In addition to this concept, secondary thrombosis has been attributed to fall in systemic blood pressure after infarction especially with cardiogenic shock.[20] This reduction in arterial pressure would be augmented by coronary arteriosclerotic narrowing.[21] Additional factors which have been suggested are release of thromboplastic substances from necrotic muscle endothelial damage, alteration in hemodynamic blood flow in the area of infarction, enlargement of the heart, size of infarct, and length of survival time.[22]

Summary

Evidence is presented which suggests that it is likely that vasospasm initiates coronary artery thrombosis. Spasm causes a violent constriction of the vessel and also produces stasis, and both factors are implicated in the thrombotic process.

Spasm can occur in sclerotic segments, and intimal tears and plaque ruptures in arteriosclerotic plaques are attributed to spasm. The thrombus forms over the intimal disruption, abetted by the stasis of spasm. In arteries with mild or no intimal injury continuing stasis over a period of time is considered as the major factor in thrombus formation. This ongoing stasis is attributed to an injury–spasm reaction to necrotic muscle, and probably is equivalent to the "no-reflow" phenomenon of infarction.

Addendum

After this paper was submitted, direct evidence for the spastic cause of coronary artery thrombosis was reported. In an autopsied case of acute myocardial infarction, Maseri and his colleagues[24] found a fresh coronary thrombus in an arterial segment that shortly before death was observed to be in spasm by angiography

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Predictive value of electrocardiographic patterns in localizing left ventricular asynergy in coronary artery disease

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The imperfect relationship between the ECG pattern of transmural myocardial infarction (ECG MI) and the presence of myocardial infarction or scar at autopsy has been recognized.[1-] With the increasing use of coronary angiography and left cineventriculography it has become possible to examine the correlation between ECG-MI and left ventricular asynergy in populations of patients with coronary artery disease.[4-] There has been only one study[3] that has evaluated this relationship using biplane cineventriculography The remaining studies have been limited to single plane, RAO view of the left ventricle and none have systematically examined for a correlation between true posterior ECG MI and posterior asynergy The current study was therefore designed to examine the following (1) the predictive value of anterior and inferior patterns of ECG-MI in localizing asynergy as assessed by biplane RAO/LAO left cineventriculography (2) the correlation of currently accepted criteria of true posterior ECG MI[11] with posterior asynergy and (3) the value of biplane vs single-plane left cineventriculography in assessing regional asynergy

Methods

1 Study population. The study population consisted of 200 consecutive patients undergoing biplane left cineventriculography who demonstrated coronary artery disease, defined as ≥ 70 per cent luminal narrowing of at least one major coronary vessel. This group did not include any patient with ECG evidence of left or right bundle branch block, left anterior or posterior hemiblock, left or right ventricular hypertrophy or preexcitation syndrome.

2. ECG analysis. The majority of electrocardiograms were obtained within 24 hours prior to catheterization. Of the various patterns generally accepted as indicative of transmural infarction, the following criteria for infarction were employed.

A. Anterior ECG-MI. Any of the following were accepted as evidence of anterior infarction.

Anteroseptal. QS deflections or Q waves $\geq .04$ sec. in Leads V to V, depth of Q wave > 25 per cent of the following R wave, if present.

Anteroapical. QS deflections or Q waves $\geq .04$ sec. in Leads V to V, depth of Q wave > 25 per cent of the following R wave, if present.

Anterolateral. QS deflections or Q waves $> .04$ sec. in Leads I, V to V, depth of Q wave > 15 per cent of the following R wave, if present.

Poor R wave progression R wave < 2 mm. in Lead V, R wave < 4 mm. in Lead V.

Reversed R wave progression. decrease in R wave amplitude from one precordial lead to the next.

B. Inferior ECG-MI Q wave $\geq .04$ sec. in Lead aV_F, depth of Q wave > 25 per cent of the following R wave, if present.

C. True posterior ECG-MI For initial analysis, an R wave $\geq .04$ sec. in Lead V was used as evidence of posterior infarction. Subsequent analysis used combinations of the following criteria[11]

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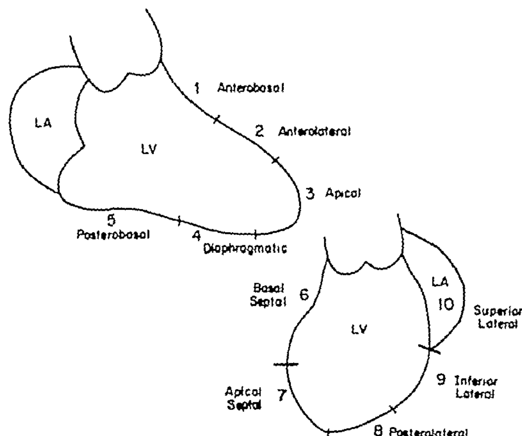


Fig 1 Nomenclature for biplane left cineventriculography of the Collaborative Studies in Coronary Artery Surgery (CASS)

R wave ≥ 04 sec in Leads V or V_6 an R/S o ≥ 1 in Leads V or V_2 and an upright T ave in Lead V

3 Ventriculographic analysis Biplane 30 degree RAO/60 degree LAO left cineventriculography was carried out in all patients. Segmental wall analysis was performed using the nomenclature and grading system of the Collaborative Studies in Coronary Artery Surgery (CASS) (Fig. 1) Asynergy was graded as moderate hypokinesis, severe hypokinesis, akinesis, dyskinesis, or aneurysm, and was localized to anterior inferior or posterior regions. For the purpose of this study from Fig. 1 segments 1 2, 3 6, and 7 were considered anterior segments 4 and 5 inferior and segments 8 and 9 posterior Segment 10 was not used in the analysis

4 Statistical analysis The value of each of the various ECG-MI patterns to predict and correctly localize asynergy was analyzed by identifying

True Positives (TP) = + ECG + asynergy
True Negatives (TN) = – ECG – asynergy
False Positives (FP) = + ECG – asynergy
False Negatives (FN) = – ECG/+ asynergy
and determining:

Sensitivity = $\frac{TP}{TP + FN}$ (the fraction of all patients with asynergy who had evidence of corresponding ECG MI)

Sensitivity = $\frac{TN}{TN + FP}$ (the fraction of all patients without asynergy who did not have evidence of ECG MI)

Predictive Accuracy = $\frac{TP}{TP + FP}$ (the fraction of all patients with evidence of ECG MI who had correctly localized asynergy)

Results

1 Predictive value of ECG-MI in localizing asynergy (Table I)

A Overall. From the group of 200 patients with established CAD 152 had asynergy of at least one segment (76 per cent) There were 103 ECG MI patterns in a total of 84 patients, which were distributed as follows isolated anterior—31 isolated inferior—25 isolated posterior—nine, combined anterior and inferior—13, combined

Table I Correlation of ECG MI with asynergy

	Sensitivity	*Specificity*	*Predictive accuracy*
Overall	78/152 (51%)	42/48 (88%)	78/84 (93%)
Anterior	43/118 (36%)	81/82 (99%)	43/44 (98%)
Inferior	36/103 (35%)	89/97 (92%)	36/44 (82%)
Posterior	11/92 (12%)	104/108 (96%)	11/15 (73%)
*Posterior**	11/69 (16%)	83/87 (95%)	11/15 (73%)

*Excluding 44 patients with evidence of anterior ECG-MI.

Table II Correlation of ECG-MI with varying degrees of asynergy

	Sensitivity	*Specificity*	*Predictive accuracy*
Overall			
A	78/152 (51%)	42/48 (88%)	78/84 (93%)
B	65/103 (63%)	75/99 (80%)	65/84 (77%)
C	54/79 (68%)	91/120 (76%)	54/84 (68%)
Anterior			
A	43/118 (36%)	81/82 (99%)	43/44 (98%)
B	40/80 (50%)	116/120 (97%)	40/44 (91%)
C	36/65 (55%)	127/135 (94%)	36/44 (82%)
Inferior			
A	36/103 (35%)	89/97 (92%)	36/44 (82%)
B	25/46 (54%)	134/154 (87%)	25/44 (57%)
C	15/20 (75%)	151/180 (84%)	15/44 (34%)
Posterior			
A	11/69 (16%)	83/87 (96%)	11/15 (73%)
B	7/33 (21%)	115/123 (94%)	7/15 (47%)
C	6/21 (29%)	126/133 (95%)	6/15 (40%)

A = All degrees of asynergy (moderate hypokinesis to aneurysm included).
B = Severe hypokinesis, akinesis, dyskinesis, or aneurysm only
C = Akinesis, dyskinesis, or aneurysm only

inferior and posterior—six. Of the 152 patients with asynergy 78 had evidence of ECG MI, for a sensitivity of 51 per cent. Of the 48 patients without asynergy there were eight false-positives with evidence of ECG-MI for a specificity of 88 per cent. Of 84 patients with ECG-MI, 78 had correctly localized asynergy giving a predictive accuracy of 93 per cent.

B. Anterior There were 118 patients with anterior asynergy of whom 43 had evidence of anterior ECG-MI for a sensitivity of 36 per cent. Of the 82 patients without anterior asynergy only one patient had evidence of anterior ECG-MI for a specificity of 99 per cent. Of the 44 patients with evidence of anterior ECG MI, 43 had anterior asynergy on the ventriculogram, giving a predictive accuracy of 98 per cent.

Table III Correlation of criteria for true posterior ECG-MI with posterior asynergy

	Sensitivity	*Specificity*	*Predictive accuracy*
R_1	11/69 (16%)	83/87 (95%)	11/15 (73%)
R_1 + T	8/69 (12%)	85/87 (98%)	8/10 (80%)
R_1 + R/S	6/69 (9%)	83/87 (95%)	6/10 (60%)
R_1 + R/S + T	4/69 (6%)	85/87 (98%)	4/6 (67%)
R_2	24/69 (35%)	53/87 (61%)	24/58 (41%)
R_2 + T	15/69 (22%)	72/87 (83%)	15/30 (50%)
R_2 + R/S	7/69 (10%)	74/87 (85%)	7/20 (35%)
R_2 + R/S + T	3/69 (4%)	81/87 (93%)	3/9 (33%)
R_{1+2}	35/69 (51%)	49/87 (56%)	35/73 (48%)
R_{1+2} + T	23/69 (33%)	70/87 (80%)	23/40 (58%)
R_{1+2} + R/S	13/69 (19%)	70/87 (80%)	13/30 (43%)
R_{1+2} + R/S + T	7/69 (10%)	79/87 (91%)	7/15 (47%)

Patients with anterior ECG-MI were excluded from the analysis.
R_1 = an R wave ≥ .04 sec. in Lead V_1
R_2 = an R wave ≥ .04 sec. in Lead V_2
R_{1+2} = an R wave ≥ .04 sec. in Leads V_1 or V_2
R/S = an R/S ratio ≥ 1 in Leads V_1 or V_2
T = an upright T in Lead V_1

C Inferior There were 103 patients with inferior asynergy of whom 36 had evidence of inferior ECG MI, for a sensitivity of 35 per cent. Corresponding specificity and predictive accuracy for this group were 92 per cent and 82 per cent, respectively

D Posterior There were 92 patients with posterior asynergy of whom 11 had evidence of true posterior ECG MI (.04 sec. R wave in Lead V_1), for a sensitivity of 12 per cent. Corresponding specificity and predictive accuracy for this group were 96 per cent and 73 per cent, respectively The presence of an anterior ECG-MI could mask an accompanying true posterior ECG-MI. If patients with anterior ECG-MI are excluded from the analysis of the true posterior group, this eliminates 44 patients, leaving 69 patients with posterior asynergy and 87 patients without posterior asynergy for evaluation. Analysis of this group yielded a sensitivity of 16 per cent, a specificity of 95 per cent, and a predictive accuracy of 73 per cent.

II Correlation of ECG-MI with varying degrees of asynergy The values presented for sensitivity specificity and predictive accuracy were derived from ventriculographic estimation of asynergy ranging from moderate hypokinesis to dyskinesis and aneurysm. If one alters the criteria for

Table IV Value of LAO projection in assessing regional asynergy

	Anterior	*Inferoposterior*
LAO > RAO	20/118 (17%)	36/122 (30%)
LAO ≢ RAO	7/118 (6%)	10/122 (8%)

LAO > RAO = greater degree of asynergy on LAO than RAO.
LAO ≢ RAO = asynergy noted only on LAO.

Table V Value of LAO projection in assessing regional asynergy in subset with ECG MI

	Anterior	*Inferoposterior*
LAO > RAO	6/43 (14%)	11/41 (27%)
LAO ≢ RAO	0/43 (0%)	3/41 (7%)

LAO > RAO = greater degree of asynergy on LAO than RAO.
LAO ≢ RAO = asynergy noted only on LAO.

asynergy to include only the more severe degrees of wall motion abnormality then the correlation with ECG MI will change accordingly This relationship was examined as follows (Table II)

A. All degrees of asynergy (moderate hypokinesis to aneurysm included)

B. Severe hypokinesis, akinesis, dyskinesis, or aneurysm only

C Akinesis, dyskinesis, or aneurysm only

As can be seen in Table II in each group the sensitivity increases while specificity and predictive accuracy decrease when more severe degrees of asynergy are used. The changes are most marked in the inferior and posterior groups, and less marked in the anterior group. For example, if one compares asynergy criteria A with C predictive accuracy decreases from 82 per cent to 34 per [illegible] in the inferior group and from 73 per cent to [illegible] per cent in the posterior group while decreasing only to 82 per cent from 98 per cent in the anterior group

Changes of similar magnitude occur in the opposite direction for sensitivity Specificity is least affected in all groups.

III Correlation of criteria for true posterior ECG MI with posterior asynergy The correlation of true posterior ECG MI with posterior asynergy as determined from the LAO left cineventriculogram was initially derived using an R wave of .04 sec in Lead V as the sole ECG criterion of posterior infarction. We then employed other accepted criteria of true posterior ECG MI and examined similar correlations with posterior asynergy Combinations of the following criteria were used

1. R wave ≥ .04 sec in Lead V [illegible] (R [illegible]) in Lead V [illegible] (R_1) or in either Leads V [illegible] or V [illegible] (R [illegible])
2. R/S ratio ≥ 1 in Lead V [illegible] or V [illegible] (R S)
3. Upright T waves in Lead V [illegible] (T)

Table III lists the values for sensitivity specificity and predictive accuracy of these various criteria. Sensitivity ranged from 4 per cent to 51 per cent, being lowest in the R_1 group and highest in the $R_{[illegible]}$ group. Specificity varied from 56 per cent to 98 per cent, with the highest values recorded in the R group. Predictive accuracy ranged from 33 per cent to 80 per cent, being lowest in the R_1 group and highest in the $R_{[illegible]}$ group.

IV Value of biplane vs single plane left cineventriculography in assessing regional asynergy In this same group of patients the value which the 60 degree LAO projection adds to the 30 degree RAO projection in evaluating regional asynergy was examined. In this analysis asynergy was localized to anterior (RAO segments 1,2,3,/LAO segments 6,7) and inferoposterior (RAO segments 4,5/LAO segments 8,9) regions (Fig. 1) The presence of a greater degree of asynergy on the LAO than on the RAO and the presence of asynergy only on the LAO were noted. Of 152 patients with asynergy greater asynergy on the LAO than RAO occurred in 22 (14 per cent) and asynergy only on the LAO in four (3 per cent) Analysis of asynergy by specific regions is shown in Table IV Greater asynergy on the LAO than RAO occurred in 17 per cent of patients with anterior asynergy and in 30 per cent of patients with inferoposterior asynergy Corresponding values for asynergy only on the LAO were 6 per cent for anterior and 8 per cent for inferoposterior The subset of asynergy and accompanying ECG MI was also examined. Of 78 patients with asynergy and associated ECG-MI, greater asynergy on the LAO than RAO occurred in 12 (15 per cent) and asynergy only on LAO in 0 (0 per cent) Analysis of asynergy and ECG MI by specific regions is shown in Table V Greater asynergy on the LAO than RAO occurred in 14 per cent of patients with anterior asynergy and anterior ECG MI, and in 27 per cent of patients with inferoposterior asynergy and inferior or posterior ECG MI.

Table VI Studies of the correlation of ECG MI with asynergy

Reference No.	Sensitivity	Specificity	Predictive accuracy
Overall 1	253/416 (61%)	682/768 (89%)	253/339 (75%)
2*	29/53 (55%)	38/55 (69%)	29/48 (60%)
3	72/84 (86%)	35/39 (90%)	73/77 (95%)
4	77/156 (49%)	–	–
7	65/100 (65%)	–	–
8	61/119 (51%)	73/76 (96%)	–
10	–	–	163/225 (72%)
Current	78/162 (48%)	42/48 (88%)	78/84 (93%)
Anterior 3	–	–	40/40 (100%)
4	17/32 (53%)	–	–
6	–	–	50/55 (90%)
8	–	76/76 (100%)	29/30 (97%)
9	68/102 (67%)	–	–
10	–	–	67/82 (84%)
Current	43/118 (36%)	81/82 (99%)	43/44 (98%)
Inferior 3	–	–	19/28 (68%)
4	50/80 (63%)	–	–
5	–	–	40/52 (77%)
6	–	–	73/82 (89%)
8	–	73/78 (94%)	25/33 (76%)
10	–	–	56/100 (56%)
Current	36/103 (35%)	89/97 (92%)	36/44 (82%)
Posterior 3	–	–	3/5 (60%)
4	6/38 (16%)	–	–
Current	11/69 (16%)	83/87 (96%)	11/15 (73%)

*Studies No. 1 and No. 2 correlate ECG MI with infarct or scar at autopsy

Corresponding values for asynergy only on the LAO were 0 per cent for anterior and 7 per cent for inferoposterior

Discussion

I Predictive value of ECG-MI in localizing asynergy The correlation of ECG MI with asynergy as assessed in the present study (Table I) indicates that ECG-MI has a high predictive accuracy (anterior > inferior > posterior) and specificity but low sensitivity for localizing asynergy Thus, in a patient with established CAD and the pattern of an anterior inferior or true posterior ECG MI the likelihood of corresponding regional asynergy is substantial, and ranges from 73 per cent to 93 per cent. Values obtained from prior studies (both autopsy and clinical) appear in Table VI along with the data obtained in the current study In general, there is good agreement in the values for predictive accuracy and specificity The greatest discrepancy appears in the values for sensitivity of anterior and inferior ECG MI which are lowest in the present study The differences between studies can probably be explained on the basis of the following factors.

1. Most importantly the criteria for asynergy which vary from study to study have a significant effect upon the values obtained for predictive accuracy and sensitivity as noted in Table II. The use of only severe degrees of asynergy to establish a positive correlation with ECG-MI will increase the sensitivity and decrease the predictive accuracy compared to values obtained when all degrees of asynergy are used. Values for sensitivity of anterior and inferior ECG-MI increase to 56 per cent (from 36 per cent) and to 45 per cent (from 35 per cent) respectively when only severe degrees of asynergy are used. These values then compare quite favorably with values obtained from prior studies. These changes in sensitivity and predictive accuracy are most marked with inferior and true posterior ECG MI and are least marked with anterior ECG MI. The reason for this finding is that patients with anterior ECG-MI in general have more severe

degrees of asynergy than those with inferior or true posterior ECG MI and this group is therefore least affected by a change in the criteria for asynergy

2. The present study correlates ECG MI with asynergy in the corresponding region. Some of the previous studies have not specified that the area of asynergy correlate anatomically with the location of ECG MI, and this would tend to increase sensitivity and predictive accuracy

3. The use of single-plane left cineventriculography in all but one of the prior studies[3] limits the appreciation of asynergy of the septum and posterior wall, which can be viewed only on the LAO projection. This will affect the correlation, most specifically with posterior ECG MI.

4. The more stringent the criteria for ECG MI, the lower the sensitivity and the higher the predictive accuracy

5. The inclusion of patients whose ECG shows a conduction abnormality or hypertrophy pattern will impair the ability to diagnose ECG MI, and hence alter the correlation with asynergy All such patients were excluded in the present study but exclusions vary greatly among the prior studies.

II Correlation of criteria for true posterior ECG-MI with posterior asynergy The value of [illegible]ous criteria of true posterior ECG MI in [illegible]cting posterior asynergy is noted in Table III. It can be seen that R and its combinations yield the highest predictive accuracy and specificity but are at the same time the least sensitive. R_1 + T is the combination most predictive of posterior asynergy (80 per cent) In contrast, some of the R_2 group (R_2, R + T) are more sensitive, but with decreased specificity and predictive accuracy R is the most sensitive of all the criteria examined. R + T appears to optimize sensitivity and predictive accuracy for posterior asynergy In general, for this group of patients with established CAD

1. One out of two patients with posterior asynergy had an R wave in Leads V or V on their ECG

2. Only one out of 20 patients without posterior asynergy had an R wave in Lead V on their ECG and

3. Three out of four patients wh had an R wave in Lead V on their EC[illegible] demonstrated posterior asynergy on the LAO [illegible]ntriculogram.

Accordingly in clinical pra[illegible] e would recommend the use of an R wave in Lead V particularly when accompanied by an upright T wave in Lead V as the best ECG criteria for predicting posterior wall asynergy in patients with CAD

III Value of biplane vs single plane left cineventriculography in assessing regional asynergy In a previous study[13] which compared biplane and single plane left cineventriculograms, 50 patients with CAD were evaluated. Thirty five patients demonstrated asynergy in the RAO projection, and no patient had isolated asynergy in the LAO view There is no information regarding the degree of asynergy in the various projections in this study The value of the LAO projection for assessing regional asynergy in the present study is noted in Tables IV and V For the entire population of 152 patients with asynergy 22 (14 per cent) demonstrated more extensive asynergy in the LAO than in the RAO view In only four (3 per cent) was asynergy seen solely in the LAO view When analyzing the inferoposterior region, however the LAO demonstrated asynergy not appreciated in the RAO in 8 per cent of cases and enhanced assessment of asynergy in 30 per cent of cases. It can be noted from the tables that the relative value of the LAO is greater in assessing inferoposterior than anterior asynergy However, even in patients with anterior asynergy 6 per cent had asynergy noted solely on the LAO projection. Thus the LAO view makes a small but important contribution to the assessment of regional asynergy and would appear to justify the routine use of biplane left cineventriculography in the evaluation of patients with coronary artery disease

Summary

Transmural myocardial infarction by ECG (ECG MI) was correlated with left ventricular asynergy by biplane left cineventriculography in 200 patients with coronary artery disease. The ability of individual ECG MI patterns to predict and correctly localize asynergy was anterior—98 per cent (43 of 44) inferior—82 per cent (36 of 44), true posterior—73 per cent (11 of 15) Of various combinations of criteria for true posterior ECG MI, the pattern of an R wave and upright T wave in Lead V was most predictive of posterior asynergy—80 per cent (8 of 10). The LAO projection demonstrated a wall motion abnormality not appreciated in the RAO in 8 per cent (10 of 122) of

ses of inferoposterior asynergy and enhanced ssessment of asynergy in 30 per cent (36 of 122) f cases. It is concluded that (1) ECG-MI has a igh predictive accuracy for left ventricular synergy (2) an R wave and upright T wave in ead V is the best ECG predictor of posterior synergy and (3) the LAO projection makes an nportant contribution to the assessment of egional asynergy in coronary artery disease.

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Echocardiographic LV function in thyrotoxicosis

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The clinical cardiovascular effects of thyrotoxicosis are well known, but there is little detailed information relating to the effect of thyrotoxicosis on left ventricular (LV) and other cardiac chamber size in man, on LV contractility and to the changes in LV function after palliative and definite treatment of the thyrotoxic state.

Echocardiography is a simple non invasive method for studying cardiac structure and function. We have used it to study LV function in a group of patients with untreated thyrotoxicosis and to measure the changes in LV contractility which occur after treatment with a beta adrenergic blocking drug and after treatment with antithyroid drugs.

Patients

Studies were made in 11 consecutive patients with thyrotoxicosis who were in sinus rhythm. The patients were females and their age ranged from 23 to 46 years. The clinical and biochemical data are given in Table I Clinical evidence of thyrotoxicosis was present in all the patients. most of them had important weight loss and a fine tremor and eye signs were present in eight. Biochemical tests confirmed the diagnosis the T3 sephadex, serum T4I and free thyroxine index were greatly elevated in all but one patient (patient No 9) who had mild thyrotoxicosis. Patient No 1 was in clinical cardiac failure with an elevated jugular venous pressure She received digoxin (0.25 mg. daily) throughout the study period. The JVP was also increased in patient No. 3, but she did not have clinical cardiomegaly or additional heart sounds. A third heart sound was present in four patients and an ejection systolic murmur (grade 1-3/6) at the left sternal border was present in six patients. In one patient, a Means-Lerman scratch" was heard in the second to third left intercostal space.

Methods

Protocol A full clinical and biochemical examination was performed in the untreated thyrotoxic state (control) Systemic blood pressure was measured using a Baumanometer Echocardiography was performed and the systolic time intervals recorded. Patients were then treated in two ways, according to the discretion of the attending physician

1 Eight patients received propranolol (60 to 120 mg. per day in three divided doses) The non-invasive study was repeated 4 days after the onset of treatment.

2. All patients were subsequently treated with anti thyroid drugs (methimazole or propylthiouracil) and the cardiac studies were made on two further occasions 2 to 4 weeks after the onset of treatment with these (AT1) and after 2 to 3 months of this treatment (AT2) Before the last set of measurements were made propranolol was stopped in patients who received it initially

The protocol was not completed in three patients including the ill patient (case No. 1). Their thyroid status relapsed because they did not take their drugs (poor patient compliance).

Echocardiography Echocardiograms were recorded with an Ekoline 20A echocardiograph

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Table I Clinical findings (prior to treatment)

Patient	*Age*	*Sex*	*Weight loss*	*Tremor*	*Eye signs*	*T uptake (%)*	*T (μg/100 mL)*	*FTI*	*JVP*	*Edema*	*Large LV*	S_3	S_4	*Murmurs*
1	43	F	++	+	−	60	14.0	17.5	4 cm	0	+	−	+	SM
2	32	F	++	+	+	65	10.4	14.5	0	0	−	−	−	SM
3	23	F	++	+	+	69	10.3	16.0	4 cm	0	−	−	−	SM
4	28	F	+	+	+	84	17.0	30.0	0	0	−	+	−	Means-Lerman scratch
5	48	F	+	+	+	70	11.8	16.7	0	0	−	+	−	−
6	34	F	±	−	+	57	10.4	12.0	0	0	−	−	−	−
7	33	F	±	+	+	64	9.8	13.2	0	0	−	−	−	−
8	30	F	+	+	−	44	16.5	15.2	0	0	−	−	−	SM
9	24	F	±	+	−	62	8.5	8.6	0	0	−	+	−	SM
10	46	F	+	+	+	66	9.0	10.5	0	0	−	+	−	−
11	46	F	++	+	+	79	14.3	22.5	0	0	−	−	−	SM

FTI = free thyroxine index; JVP = jugular venous pressure (cm. above sternomanubrial angle); S_3 = third heart sound; S_4 = fourth heart sound; SM = systolic murmur.

(Smith Kline Instruments) coupled to a VR-6 *Electronics for Medicine photographic strip chart* recorder. A 2.25 MHz transducer was used and this was focused at 7.5 cm. Recordings were made with the patient in a semi-supine anteroposterior or a 20 degree left anterior oblique position. The left ventricular (LV) and right ventricular (RV) dimensions were recorded with the echo beam in the standard plane: the interspace selected was that in which the mitral valve could be recorded *with the transducer perpendicular to the chest* wall and the LV was measured at the level of the free edge of the mitral leaflets. These maneuvers guard against foreshortening of the measured diameter of the LV (minor axis). The echo beam was then directed to record the other intracardiac structures and chambers.

The *LV dimension* (minor diameter) was measured at end-diastole (Dd) and at end-systole (Ds) (Fig. 1). The *percentage shortening of the LV* diameter during systole (%ΔS) was calculated, where

$$\%\Delta S = \frac{Dd - Ds}{Dd} \times 100\%$$

LV volumes were calculated from the cube of diameter measurements and were indexed for body surface area. Echocardiographic *stroke index* (SI) was the difference between LV end diastolic and end-systolic volume (indexed) and *cardiac index* (CI) was calculated by multiplying SI by heart rate (HR). *LV wall thickness* and the thickness of the *interventricular septum* (IVS) were measured at end-diastole.

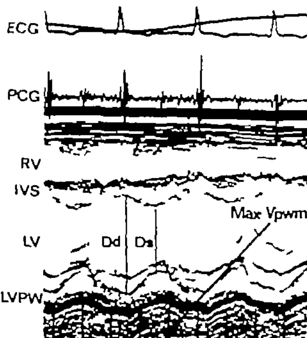


Fig. 1 Echocardiogram of the left ventricle (*LV*). Ventricular dimensions were measured at end-diastole (*Dd*) and end-systole (*Ds*). *Max Vpwm* = maximum velocity of posterior wall motion.

The mean velocity of circumferential fiber shortening (mean Vcf) was calculated,[9, 10] where

$$\text{mean Vcf} = \frac{\%\Delta S}{\text{LVET}} \times 100 \text{ (circ./sec.)}$$

and LVET is the left ventricular ejection time measured from the carotid pulse tracing. *Maximum velocity of posterior wall motion* (max

Table II Echocardiographic measurements

	Thyrotoxicosis	*Propranolol*	*Antithyroid drugs*					*Normal range*
			p	*2-4 weeks*	*p*	*2-3 months*	*p*	
LV Dd (cm.)	4.6 ± 0.6	4.7 ± 0.7	ns	4.6 ± 0.4	ns	4.5 ± 0.4	ns	3.9-4.4
Ds (cm.)	2.8 ± 0.6	2.8 ± 0.6	ns	2.6 ± 0.2	ns	2.6 ± 0.3	ns	–
%ΔS	40 ± 6	40 ± 4	ns	43 ± 4	ns	37 ± 4	< 0.01	31-39
Mean Vcf (circ./sec.)	1.60 ± 0.32	1.57 ± 0.19	ns	1.64 ± 0.25	ns	1.31 ± 0.23	< 0.05	1.05-1.45
Max Vpwm (mm./sec.)	71 ± 13	66 ± 10	ns	54 ± 11	< 0.05	46 ± 14	< 0.01	45-62
SI (ml./M.²)	63 ± 18	59 ± 20	ns	55 ± 21	ns	47 ± 15	ns	40-54
CI (L./min./M.²)	5.0 ± 1.6	5.0 ± 1.8	ns	3.8 ± 2.1	ns	3.3 ± 1.0	< 0.01	2.8-4.2
Heart rate (beats/min.)	96 ± 14	84 ± 11	< 0.001	75 ± 5	< 0.01	68 ± 6	< 0.001	–
LVPW (cm.)	0.6 ± 0.2	0.6 ± 0.9	ns	0.6 ± 0.1	ns	0.7 ± 1.0	ns	0.5-1.0
IVS (cm.)	0.9 ± 0.2	0.9 ± 0.2	ns	0.8 ± 0.2	ns	1.0 ± 0.1	ns	0.6 ± 1.1
LA diam. (cm.)	2.8 ± 0.4	3.0 ± 0.5	ns	3.1 ± 0.2	ns	2.8 ± 0.5	ns	2.0-3.8
RVID (cm.)	2.2 ± 0.2	2.1 ± 0.4	ns	2.3 ± 0.6	ns	2.7 ± 0.4	ns	0.9-2.6
Ao (cm.)	2.7 ± 0.5	2.5 ± 0.3	ns	2.6 ± 0.3	ns	2.3 ± 0.4	< 0.05	2.0-3.7
Mitral EF slope (mm./sec.)	96 ± 22	104 ± 23	ns	99 ± 13	ns	101 ± 33	ns	> 60

See text for details of indices and abbreviations.
p values—comparison with values in untreated state.

Vpwm) was the steepest tangent to the endocardial surface of the posterior LV wall during ystole

The *right ventricular internal dimension* (RVID) was measured through the R wave of the QRS complex. *The aortic root diameter* was measured at the end of ventricular diastole. *Left atrial (LA) dimension* was measured at end ventricular systole.

The diastolic closure rate (EF slope) of the *anterior mitral leaflet* (AML) was measured. The EF slope was essentially monophasic when recorded at a paper speed of 50 mm./sec. so that there was no ambiguity in measurement. The mitral EF slope is related to early diastolic compliance of the left ventricle in the absence of mitral valve disease

Systolic time interval measurements. The time intervals of the cardiac cycle were recorded on the Electronics for Medicine VR6 photographic recorder at a paper speed of 100 mm./sec. A simultaneous electrocardiogram (ECG) phonocardiogram (PCG) and apexcardiogram (ACG) or carotid pulse tracing were recorded using a piezoelectric crystal transducer The mean measurements over several respiratory cycles were used in the analysis of both the echocardiogram and systolic time interval recordings.

Pre-ejection period (PEP) is the time interval from the onset of the QRS complex of the ECG till aortic valve opening, which corresponds to the upstroke of the carotid pulse tracing after correction for pulse transmission time delay *Isovolumic contraction time* (ICT) was measured from the onset of the upstroke of the apex cardiogram (U_{ACG}) to the moment of aortic valve opening[11]

$$ICT = PEP - (Q_{ICG} - U_{ACG}) \text{ msec.}$$

PEP and ICT are related to velocity measurements of LV contractility but also depend on preload and afterload.[13]

Left ventricular ejection time (LVET) was measured from the upstroke of the carotid pulse tracing to the nadir of the dicrotic notch. LVET depends on stroke volume, afterload and myocardial contractility Since both PEP and LVET are heart rate-dependent, we calculated ΔPEP and ΔLVET from data of Weissler and associates, where the Δ value is the difference between the observed time interval measurement and the predicted normal at a given heart rate.

The ratio PEP/LVET was calculated. This measurement is less dependent on heart rate,

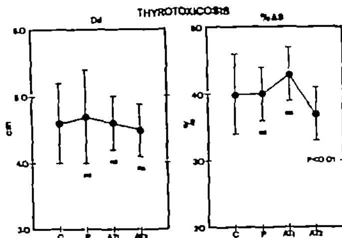


Fig. 2. Left ventricular end-diastolic diameter (*Dd*) and percentage shortening during systole (%ΔS) in thyrotoxicosis (*C*), on propranolol (*P*), and early (2 to 4 weeks) (*AT1*) and late (2 to 3 months) (*AT2*) after the onset of treatment with definitive anti-thyroid (AT) drugs. LVDd is normal in size and does not change throughout the study. %ΔS is increased initially and does not change on propranolol, it decreased int the normal range (*shaded area*) 2 to 3 months after the commencement of treatment with antithyroid drugs.

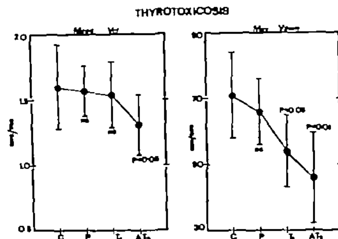


Fig. 3. Mean velocity of circumferential fibre shortening (*Vcf*) and maximum velocity of posterior wall motion (*Vpwm*) before (*C*) and after treatment with propranolol (*P*) and antithyroid drugs (Early *AT1* Late *AT2*). Mean Vcf and max Vpwm are increased in thyrotoxicosis, do not change after propranolol, and decrease into the range of normal (*shaded area*) when the patients become euthyroid (*AT2*).

magnifies abnormalities of ventricular contractility and is related to LV ejection fraction.[18] *Total electromechanical systole (Q-A$_2$)* was the sum of PEP and LVET ΔQ-A$_2$ is the rate corrected value.

Isovolumic relaxation period (IRP) was measured as the time interval from aortic valve closure (A_2 on the PCG) to the onset of mitral valve opening (D point) on the echocardiogram of the anterior mitral leaflet.

Statistical analysis. Statistical analysis was made using Student's t test for paired data, each patient served as his own control.

Results

Echocardiographic measurements. The echocardiographic data are summarized in Table II.

In the *untreated thyrotoxic state* the left ventricle was normal in size in all but 1 patient (case No. 1) and contracted very well. %ΔS was high and the velocity measurements mean Vcf and max Vpwm were increased (Figs. 2 and 3). LV wall thickness was normal. In patient No. 1 the LV was enlarged (Dd 6.0 cm.) and %ΔS (25 per cent) and mean Vcf (1.00 circ./sec.) were slightly decreased. There was sinus tachycardia in all the patients (Fig. 4) and the cardiac index was high

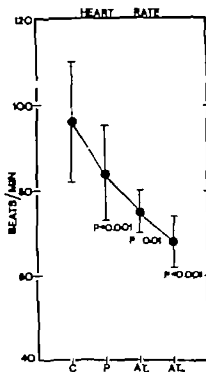


Fig. 4. Heart rate in our patients. Heart rate is increased in thyrotoxicosis (*C*), decreases on propranolol (*P*), and decreases further after treatment with definitive anti-thyroid drugs (*AT1* and *AT2*).

(Fig. 5) Echocardiographic left atrial size, right ventricular dimension, and aortic root diameter were normal. The mitral EF slope was increased and was related to the increased stroke index (Fig. 6). In the sick patient who was in severe cardiac failure (case No. 1) there was a shift to the right, EF slope was relatively low for a given stroke index.

Treatment with *propranolol* produced an immediate improvement in the patients clinical state and all who received the drug reported that they felt much better within 48 to 72 hours. Heart rate fell ($p < 0.001$) (Fig. 4) but there was no change in cardiac index· stroke index tended to increase although the difference was not significant statistically (Fig. 5) There was no change in %ΔS, mean Vcf, and max Vpwm (Figs. 2 and 3)

Antithyroid drugs did not alter LV diameter RV diameter and LA size. The aortic root diameter decreased slightly the reason was not apparent. There was a further decrease in heart rate and cardiac index fell to the range of normal after 2 to 3 months ($p < 0.001$) (Figs. 4 and 5) At this time the extent of LV shortening (%ΔS) decreased ($p < 0.01$) as did the velocity measurements of LV contraction (mean Vcf = $p < 0.05$ max Vpwm = $p < 0.01$) (Figs. 2 and 3) These changes coincided with a return of the patient to a clinical and biochemical euthyroid state; two patients were slightly hypothyroidic at the time the last measurements were made. After 2 to 4 weeks (AT1) the changes were less marked the results were inbetween those obtained in the control and in the euthyroid state. There was no change in the mitral EF slope after antithyroid drugs.

The relation between mean blood pressure and mean Vcf is shown in Fig. 7 Thyrotoxic patients had a higher mean Vcf than normal subjects for any given blood pressure. The ill patient (within square) had a relatively low Vcf. Return to the euthyroid state was accompanied by a return toward the normal blood pressure–mean Vcf curve. Three patients with severe myocarditis are shown for comparison. They have a low Vcf at any given blood pressure.

Time interval measurements. The time interval measurements are given in Table III. PEP and ΔPEP are short in *thyrotoxic* patients. ΔLVET was slightly decreased, the PEP/LVET ratio was low and ΔQ-S₂ was shortened. ICT was short and IRP was normal.

Treatment with *propranolol* was accompanied by a small increase in PEP and in the PEP/LVET ratio ($p < 0.05$) although there was not a significant change in ΔPEP or ΔLVET Both ICT and IRP decreased slightly but the differences were not significant statistically

After treatment with *antithyroid drugs* there was a marked increase in PEP and ΔPEP ($p < 0.01$) and in the PEP/LVET ratio ($p < 0.01$) ΔQ-S₂ increased into the range of normal ($p < 0.001$) ICT tended to increase ($p > 0.05$) as did IRP ($p > 0.05$).

Discussion

The study shows that in thyrotoxicosis the LV is normal in size with increased contractility %ΔS, mean Vcf and max Vpwm are high. PEP and ICT are short and the PEP/LVET ratio low Cardiac index and stoke index are increased, although the reduction in peripheral resistance which occurs in thyrotoxicosis may also contribute to the increase in cardiac output. These findings are in keeping with papillary muscle studies and animal experiments,[14-16] and with systolic time interval measurements in man,[1,2] but contrast with the hemodynamic study of Ueda, who found a dilated left ventricle with a normal

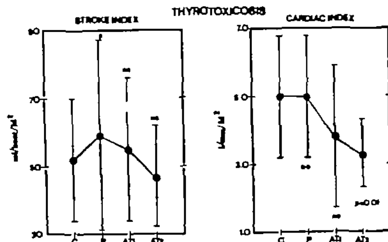


Fig. 5. Stroke index (SI) and cardiac index (CI). SI is increased in some patients initially, tends to increase further after propranolol (*P*), and then decreases again on antithyroid drugs (*AT1* and *AT2*). CI is high in the control state (*C*), does not change on propranolol (*P*), and decreases into the normal range (*shaded area*) on antithyroid drugs (*AT1* and *AT2*).

or reduced ejection fraction in patients with thyrotoxicosis. Our patients were severely thyrotoxic, but we studied young females in sinus rhythm. The only patient in our group (case No. 1) who was in clinical cardiac failure at the time of study was an older patient who had an enlarged left ventricle with relatively low contractility. The smaller increase in her mitral EF slope for her high SI probably indicates abnormal early LV diastolic compliance. Patients in severe cardiac failure, older patients, or patients with additional coronary artery disease may have dilated hearts with impaired myocardial function.

Treatment with beta blocking drugs does not alter myocardial contractility in patients with thyrotoxicosis, as has been suggested by previous studies using the more indirect method of systolic time interval measurements alone.[5] Nevertheless, the marked clinical improvement which follows the decrease in heart rate is noteworthy. The small increases observed in PEP and the PEP/LVET ratio may be related to the change in heart rate and do not necessarily indicate a change in inherent ventricular contractility. Thyroxine therefore seems to have a direct positive inotropic effect on the myocardium independent of adrenergic mechanisms. The tissues are thyrotoxic with a high oxygen demand and stroke volume tends to increase to maintain the high cardiac output following the decrease in heart rate. When definitive antithyroid drugs return the patient to a euthyroid state, myocardial contractility decreases, heart rate decreases

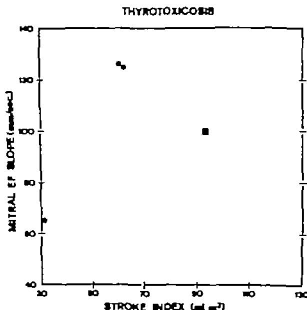


Fig. 6. Relation between stroke index and the mitral early diastolic closure rate (*EF* slope) in patients with untreated thyrotoxicosis. The EF slope increases with increasing stroke index in linear fashion. The older patient in cardiac failure (*solid square*) had a smaller increase in EF slope, suggesting reduced LV compliance.

further and the cardiac output falls to the range of normal.

A study of patients with thyrotoxicosis (before and after treatment) provides an excellent opportunity to evaluate measurements of left ventricular contractility. Mean Vcf is a good ejection phase index of myocardial contractility since it measures the velocity of ventricular ejection in

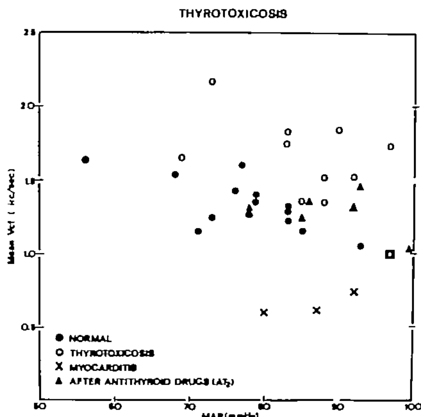


Fig. 7 Relation between mean blood pressure (*MAP*) and mean velocity of circumferential fiber shortening (*Vcf*). Patients with untreated thyrotoxicosis fall upwards and to the right of the normal curve; after treatment with definitive antithyroid drugs they shift towards the normal patients. The sick patient with cardiac failure is indicated by the square. Three patients with severe myocarditis are shown for comparison.

Table III Time interval measurements

	Normal (msec.)	Thyrotoxicosis (msec.)	Propranolol (msec.)	Propranolol P	Antithyroid drugs Early (msec.)	Antithyroid drugs P	Antithyroid drugs Late (msec.)	Antithyroid drugs P
PEP	–	63 ± 11	76 ± 10	–	81 ± 8	–	121 ± 22	–
ΔPEP	0 ± 11	−26 ± 10	−24 ± 8	ns	−19 ± 11	$p < 0.05$	+10 ± 25	$p < 0.01$
ΔLVET	0 ± 10	−11 ± 19	−23 ± 18	ns	−6 ± 10	ns	−24 ± 23	ns
ΔPEP/LVET	0.35 ± 0.04	0.37 ± 0.06	0.29 ± 0.04	$p < 0.05$	0.28 ± 0.03	ns	0.44 ± 0.11	$p < 0.01$
ΔQ-S$_2$	0 ± 14	−35 ± 21	−44 ± 19	ns	−23 ± 15	$p < 0.01$	−9 ± 22	$p < 0.001$
ICT	71 ± 16	38 ± 23	29 ± 13	ns	49 ± 25	ns	66 ± 23	ns
IRP	68 ± 13	57 ± 13	40 ± 7	ns	63 ± 13	ns	71 ± 18	ns

Δ value = deviation of observed value from predicted normal at given heart rate.

relation to the actual load against which the ventricle operates during systole (afterload).[30] We have used mean Vcf, then, to construct non-invasive force–velocity curves using mean arterial blood pressure as a simplified measurement of ventricular afterload. The concept of "afterload mismatch" in cardiac disease has been well described.

In thyrotoxicosis the blood pressure–velocity curve is shifted upwards and to the right (Fig. 7), and thus indicates a positive inotropic effect. The one sicker patient (case No. 1) had no increase in mean Vcf and this may suggest, in her, a relatively lower myocardial contractile state. Alternately her data may indicate that our curve is not shifted upwards symmetrically but is steeper at

lower levels of ventricular afterload, if this is so it makes our curve almost identical to that constructed from papillary muscle studies by Buccino and co-workers, the asymmetrical shift indicating that at least some of the effect in thyrotoxicosis is due to tachycardia. Effective treatment with antithyroid drugs returns the patients toward the normal range. We suggest that Vcf be considered in relation to some measurement of ventricular afterload when using it for the evaluation of left ventricular function. This enhances its value as a measurement of ventricular performance and can be done using a simple non invasive technique.

Summary

Serial echocardiographic studies were made in 11 patients with thyrotoxicosis. In the untreated thyrotoxic state heart rate was increased (96 ± 14 (SD) beats/minute) as were measurements of left ventricular (LV) contractility LV shortening fraction was 40 ± 6 per cent (mean $\pm$ SD) mean velocity of circumferential fiber shortening was 1.60 ± 0.32 circumferences/sec., and velocity of posterior wall motion 71 ± 13 mm./sec. Stroke index and cardiac index were increased. 52 ± 18 (SD) ml./beat per M. and 5.0 ± 1.8 (SD) liter/minute per M. respectively Cardiac chamber size was normal in all but one very ill patient and did not change during the study Treatment with propranolol, 60 mg./day produced a dramatic and immediate improvement in the clinical state of the patient. Heart rate decreased to 84 ± 11 beats/minute ($p < 0.01$) stroke index increased marginally ($p > 0.05$), and cardiac index was unaltered ($p > 0.05$) There was no change in parameters of LV contractility ($p > 0.05$) Treatment with a specific antithyroid drug (methimazole or propyl thiouracil) brought about further improvement in the clinical state and a further decrease in heart rate ($p < 0.01$) LV contractility decreased and after two to three months, when the patients were euthyroid, these measurements were in the range of normal (per cent shortening of the LV diameter 37 ± 4 $p < 0.01$, mean velocity of circumferential fiber shortening 1.31 ± 0.23 circumferences/sec., $p < 0.05$ maximum velocity of posterior wall motion, 46 ± 14 mm./sec., $p < 0.01$). Systolic time interval measurements were in keeping with these data. They showed enhanced LV performance in the control state, no change with propranolol, and they returned toward the range of normal after definitive antithyroid treatment.

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Experimental and laboratory reports

Cardiorespiratory function and extravascular lung water following acute myocardial infarction

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Oxygen administration has been part of the routine management of patients with acute myocardial infarction for many years. Its use has been justified by the almost invariable presence of arterial hypoxemia in these patients.[1-] More recent work suggests that breathing high oxygen mixtures may limit infarct size. A potential problem with this management, however is the reported increase in systemic resistance and decrease in cardiac index accompanying the inhalation of 100 per cent oxygen in patients with acute myocardial infarction,[4-] although no such changes were found by Foster and co-workers. Left ventricular filling pressures were not measured in any of these studies. A high proportion of patients with apparently uncomplicated acute myocardial infarctions have increased left ventricular filling pressures.[10] It is therefore possible that the inhalation of high oxygen mixtures may potentiate left ventricular failure in these patients.

The accessible extravascular lung water volume has been reported to be normal in patients with uncomplicated acute myocardial infarction[11,14] and normal or elevated with increasing left ventricular failure.[13-14] We report here the effects of increasing inspired oxygen mixtures on pulmonary and systemic vascular resistance, left ventricular filling pressure, cardiac index, and extravascular lung water in patients with acute uncomplicated myocardial infarction.

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Methods

We studied 11 patients between 46 and 71 years of age. All had proven acute myocardial infarction and were studied within 36 hours of admission to our Coronary Care Unit. Ten were uncomplicated on clinical grounds, while one had evidence of mild left ventricular dysfunction (S gallop). Patients with clinical or radiological evidence of severe failure, anemia, hypertension, serious dysrhythmias and those receiving cardiac medications, including anti-dysrhythmics, were excluded. None had clinical or radiological evidence of chronic pulmonary disease. Most had received morphine on admission, but low dose diazepam was the only medication allowed during this study.

After the procedure was explained and formal consent given, we passed a 7F Swan-Ganz flow directed triple lumen catheter via the antecubital vein to the pulmonary artery under continuous ECG and pressure monitoring. Pulmonary capillary wedge pressures were measured as indicators of left ventricular filling.[16] We then inserted an intravenous canula into the radial artery for systemic pressure measurements and blood sampling. With the patient supine, and with the zero reference point 5 cm. below the sternal angle,[16] we recorded pulmonary and systemic pressures using Statham P23 Db transducers on an Electronics for Medicine recorder previously calibrated in mm. Hg. After the catheters were inserted, the patients rested for 15 minutes breathing room air

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Table 1 Background information and the results of all measurements made in 11 patients with acute myocardial infarction

Patient No.	Age	Sex	Surface area (M^2)	Inspired O_2 Conc. (%)	Arterial blood gases (mm. Hg) Pa O_2	Pa CO_2	Ph (units)	Right to left shunt (%)	Mean pressures (mm. Hg) Ppw	Ppa	Pba	Cardiac index (L/min./M^2)	Pulmonary vascular resistance (units)	Systemic vascular resistance (units)	Central blood volume (ml/M^2)	EVLW (ml/M^2)
1	63	M	2.09	21	56	34	7.50		3	13	67	2.95	1.6	10.9	725	98
				35	92	27	7.52		5	13	74	2.90	1.3	12.0	745	114
				100	380	29	7.52	17.8	6	14	81	3.20	1.2	12.2	908	146
2	65	M	1.76	21	68	23	7.51		0	7	84	3.13	1.3	15.0	1055	134
				35	107	26	7.52		0	6	86	3.47	1.0	13.6	1317	132
				100	365	25	7.51	15.0	0	9	92	3.08	1.6	16.5	1096	128
3	61	M	1.82	21	40	26	7.49		3	16	62	2.79	2.8	12.2	661	139
				35		37	7.44		4	14	65	2.48	2.2	14.4	682	130
				100	275	28	7.49	28.9	6	11	71	2.70	1.0	14.5	789	166
4	46	M	2.04	21	63	24	7.56		7	21	80	3.41	1.1	11.5	725	133
				35	102	27	7.56		8	18	78	3.52	1.4	10.9	733	139
				100	370	22	7.56	16.8	6	11	78	3.66	0.7	10.7	961	156
5	61	M	2.14	21	52	29	7.51		4	12	90	3.06	1.2	12.9	769	93
				35	92	28	7.51		2	11	94	3.37	1.3	13.4	775	105
				100	445	24	7.58	15.6	7	14	113	2.99	1.1	17.7	860	96
6	60	M	2.04	21	49	27	7.42		16	23	107	2.04	1.1	17.3	809	119
				35	78	28	7.41		14	17	119	2.54	0.4	16.5	920	142
				100	315	27	7.40	13.9	15	19	118	3.17	0.6	18.2	850	147
7	66	M	2.01	21	67	33	7.48		6	10	97	2.18	0.8	18.1	778	158
				35	132	33	7.46		4	9	96	3.22	0.6	14.8	762	162
				100	420	33	7.46	16.4	6	9	97	2.76	0.5	17.5	729	122
8	55	F	1.70	21	70	29	7.50		1	8	80	2.68	1.8	17.7	618	121
				35	128	25	7.53		1	6	77	2.42	1.2	18.7	635	129
				100	405	28	7.61	13.9	0	6	81	2.29	1.6	20.8	467	118
9	58	M	1.93	21	64	27	7.54		6	14	63	2.68	1.2	19.0	765	84
				35	109	27	7.53		4	7	83	2.75	0.6	15.7	906	94
				100	375	27	7.54	16.4	7	9	89	2.62	0.4	17.8	762	111
10	60	M	2.16	21	64	27	7.49		2	8	89	3.18	0.6	13.1	778	104
				35	87	28	7.47		2	6	91	2.67	0.5	15.8	656	104
				100	475	30	7.48	9.1	1	5	92	2.50	0.7	17.0	840	91
11	71	F	1.42	21	52	26	7.56		14	21	87	1.64	3.0	37.4	570	116
				35	88	30	7.48		18	23	99	1.67	3.1	44.4	547	133
				100	305	27	7.47	20.1	20	24	99	1.49	2.8	46.8	768	140

We then measured pulmonary arterial, pulmonary capillary wedge, and radial arterial pressures, systemic and pulmonary arterial blood gases, cardiac output, central blood volume and extravascular lung water at each of three inspired oxygen mixtures selected in random order room air (21 per cent) 35 per cent (with mask) and 100 per cent (approximately with a tight fitting face mask). Rest periods of 25 to 30 minutes were given between test conditions and a further 20 minutes were allowed at each test oxygen level for equilibration to take effect. We used the standard shunt equation to estimate the magnitude of the right to-left shunt in the lungs with the patients breathing the highest oxygen mixtures. Extravascular lung water was determined using the triple indicator dilution method (cr labelled red cells, I[125] labelled albumin and Tritium enriched water) as modified by Goresky and colleagues.[11] The methods used for the analysis of the blood samples, and the subsequent calculation of cardiac output, central blood volume and extravascular lung water space have been described in detail in our earlier paper For each curve, transit times were corrected for in flow and out flow catheter delay and thus correspond to the right atrial-radial artery passage time. Relative recovery rates for each isotope averaged 100 per

cent, indicating complete recovery of the label. From the cardiac output and pressure measurements we calculated systemic and pulmonary vascular resistance as described by Wood.[20]

Results

Table I contains background patient data and the results of arterial blood gas measurements, estimated shunt flow and the pressure, flow and volume measurements at each experimental condition. Table II gives the mean values (±1 standard error) for the arterial PO_2, cardiac index, central blood volume, and extravascular lung water volume. These latter measurements have been related to body surface area for ease of comparison with previously reported studies.

All patients were hypoxemic when breathing room air (mean PaO_2 58 ± 2.5 mm. Hg). The PaO_2 remained lower than expected during 100 per cent oxygen breathing, indicating a significant shunt like effect in the lungs.

Mean cardiac index (2.89 ± .14 L./min./M.²) and central blood volume (751 ± 37 mL/M.²) were within the normal range under control conditions (room air), but the accessible lung water space (112 ± 4.3 mL/M.²) was higher than in previously reported normals (80 to 90 mL/M.²).[16, 21] The pulmonary capillary wedge pressure was normal in nine patients, borderline in one (14 mm. Hg) and only slightly elevated (16 mm. Hg) in one. These values were all well below the 20 mm. Hg reported by Yu[21] to be necessary in order to be consistently associated with an increased extravascular lung water volume. The extravascular water in the two patients with borderline or elevated capillary wedge pressures was not significantly higher than those with normal wedge pressure. There was no correlation between the wedge pressures and the extravascular lung water space measurements under any of the experimental conditions.

The changes in systemic arterial pressure, systemic vascular resistance, and cardiac index with increasing inspired oxygen mixtures are shown graphically in Fig. 1. Systemic vascular resistances and systemic pressures were different from control valves only during 100 per cent oxygen breathing ($p < 0.01$ for each case). Cardiac index fell only slightly ($p > 0.10$) and pulmonary wedge pressure did not change significantly ($p > 0.10$) with increasing inspired oxygen concentrations with the exception of patient 11 (Ppw 14 mm. Hg to 18 to 20 mm. Hg). This

Table II. Mean values, ±1 standard error for arterial PaO_2, cardiac index, central blood volume, and extravascular lung water volume measured at differing inspired oxygen concentrations

Inspired O_2 concentration (%)	*Arterial PO_2 (mm. Hg)*	*Cardiac index (L./min./M.²)*	*Central blood volume (mL/M.²)*	*Extravascular water spaces (mL/M.²)*
21	58 ± 2.7*	2.89 ± .14	751 ± 37	112 ± 4.3
35	103 ± 8.4	2.90 ± .16	776 ± 56	121 ± 5.6
100	377 ± 18.2	2.78 ± .19	793 ± 47	137 ± 9.9

*All values = mean ± S.E.

patient had the highest systemic vascular resistance and lowest cardiac index at control conditions and clearly deteriorated hemodynamically with increasing inspired oxygen mixture.

Central blood volume (Fig. 2) increased only slightly at each inspired O_2 level, but the mean increase with the highest oxygen mixture (+6 per cent) was not significant ($p > 0.05$).

Fig. 3 presents the extravascular lung water volumes under each experimental condition. During inhalation of 35 per cent oxygen, mean extravascular water volume increased 8 per cent to 121 ± 5.6 mL/M.² ($0.02 > p > 0.01$). During 100 per cent oxygen breathing the accessible water space increased further to 137 ± 9.9 mL/M.², 22 per cent higher than control volume ($p < 0.01$). The greatest increase in extravascular lung water occurred in those patients with the largest apparent intrapulmonary shunts (Fig. 4) ($p < 0.05$).

Discussion

Hemodynamics. In contrast to the frequently reported presence of increased left ventricular filling pressures in uncomplicated acute myocardial infarctions,[14] we found a normal pulmonary capillary wedge pressure in nine of 11, borderline pressure in one, and a slightly elevated pressure in only one patient. It is possible that our measurements were sufficiently delayed after the acute event for initially elevated filling pressures to return to normal levels. It is also possible that the infarction size was so small in each case that there was no left ventricular dysfunction. With increased inspired oxygen tensions, increased systemic vascular resistances contributed to increased afterload, potentially increasing left

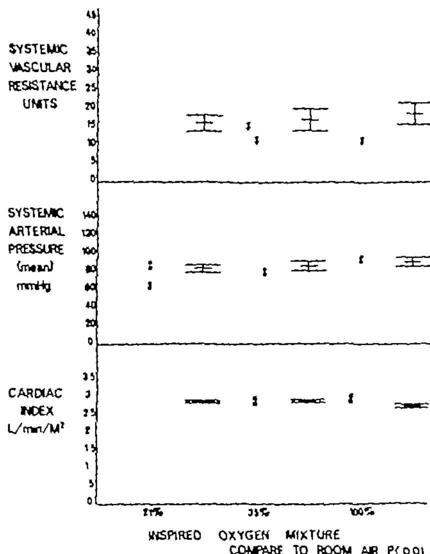


Fig. 1 Changes in systemic arterial pressure, systemic vascular resistance, and cardiac index that occur with increasing inspired oxygen mixtures. The mean values ± standard error are also shown.

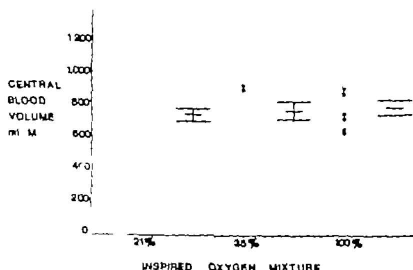


Fig. 2. Changes in central blood volume with increasing inspired oxygen mixtures with the mean ± standard error shown.

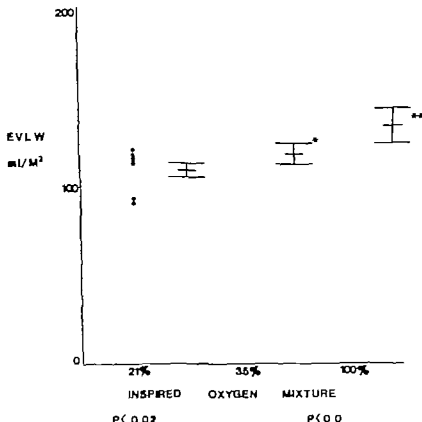


Fig. 3. Changes in accessible extravascular lung water volume with increasing inspired oxygen mixtures. The mean values ± standard errors are shown. At 35 per cent, and t 100 per cent inspired oxygen, the mean EVLW is significantly higher than that measured during room air breathing.

ventricular oxygen demand. However this was uniformly well tolerated with no significant decrease in cardiac index or change in pulmonary capillary wedge pressure. In one patient, who had a depressed cardiac index and borderline filling pressure, the increased afterload accompanying increased inspired oxygen resulted in a further decrease in cardiac index and rise in wedge pressure to 24 mm. Hg. This suggests that the administration of increased oxygen mixtures to patients with acutely compromised left ventricular function requires further investigation.

The degree of arterial hypoxemia (58 ± 2.7 mm. Hg) is lower than that previously reported in patients with acute uncomplicated myocardial infarctions in this hospital. The mechanism for this hypoxemia is unclear No patient was grossly obese, over-sedated, or unusually immobilized. It is difficult to ascribe this hypoxemia to congestion or embolization in the absence of other clinical evidence. Diffuse micro-atelectasis seems the most likely cause, perhaps related to the increased extravascular lung water

Volumes. Central Blood Volume. The right atrial to radial artery volume is a poor index of central blood volume. However the technique for measuring the pulmonary artery to left atrial volume[23] requires transeptal catheterization of the left atrium an unacceptable risk in patients with acute myocardial infarction. The mean control central blood volume (751 ± 37 ml./M.) was identical to that reported by Braunwald and Kelly[24] in resting supine normal subjects. It was also equal to the mean maximum value for central blood volume reached by our upright exercising normal subjects.[17] With increasing inspired oxygen mixtures, the mean central blood volume did not change significantly This stability might be expected since pulmonary venous pressures and blood flows did not change. Inspiration of high oxygen mixtures has no significant effect on the systemic venous capacitance vessels so that venous return is not altered.

Extravascular lung water volume. Primarily because of the variety of techniques and experimental conditions employed, considerable discus-

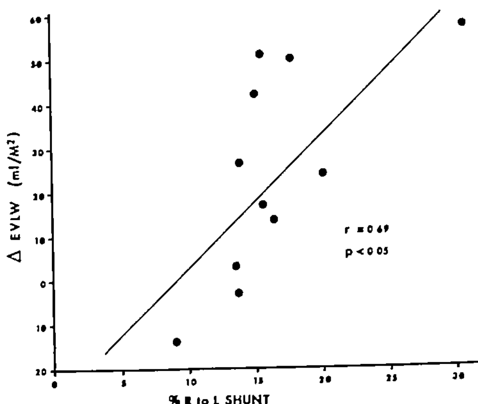


Fig. 4. The relationship of the degree of right-to-left shunt to the changes in extravascular water space measured on inspiration of 100 per cent oxygen compared to that found on room air breathing.

sion permits as to the normal" extravascular lung water volume. Luepker and colleagues have reported a group of patients from which hey selected 107 mL/M as the upper limit of normal. Using techniques identical to those reported here, we have previously reported a mean extravascular lung water space in resting upright normal subjects to be 84 ± 5 6 mL/M With increasing exercise, the accessible lung water space increased to an early plateau of 96 ± 6.4 mL/M. (range 69 to 132 mL/M) We feel that this plateau means that all available pulmonary capillaries are fully recruited so that no further areas of lung water are measured despite increasing pulmonary blood flow This value should not therefore depend on body position and should be the maximum normal value for extravascular lung water volume In the present study under control conditions (breathing room air) eight of 11 subjects exceeded our expected maximum and seven of 11 exceeded the maximum selected by Luepker and colleagues (107 mL/M.) The mean value is considerably greater than the mean maximum reached by our exercising normals. We concluded that the accessible lung water volume is el ated in our patients with apparently uncomplicated acute myocardial infarctions. The most likely cause of elevated lung water volumes is elevated pulmonary venous pressure secondary to acute alterations of left ventricular contractility and/or compliance. At least transient elevations of left ventricular filling pressure have been shown to occur on this basis in uncomplicated infarctions. Resolution of pulmonary edema is well known to trail after the resolution of elevated pulmonary venous pressure.[12, 20] It is possible that the increased lung water space measured here is on this basis. Numerous other possible causes including hypoxemia, altered capillary permeability and massive sympathetic discharge have been discussed, but never documented adequately Since this increased water volume occurs initially in the peribronchial and perivascular spaces,[20] it may alter local ventilation perfusion relationships and thus play an important role in the hypoxemia of acute myocardial infarctions.

The progressive increase in extravascular lung water volume with increasing inspired oxygen mixtures was unexpected. This increase must have occurred either through recruitment of additional capillaries so that greater space is

accessible to the indicators, or through an increased extravascular volume surrounding existing perfused capillaries. However central blood volume remained stable with increasing inspired oxygen content, and control values for extravascular water volume were higher than our maximum normal values. The pulmonary capillaries then were almost certainly maximally recruited under control conditions and no further recruitment could occur. Alterations in pulmonary capillary permeability must then be considered. Prolonged exposure to high oxygen mixture eventually leads to gross intraalveolar and interstitial edema,[17-20] but these are late changes. Perhaps the increased accessible water volume here represents the earliest manifestations of this process. West[20] has pointed out that whenever he administered enriched oxygen mixtures, some lung units became atelectatic. Capillary permeability may be altered in these areas of alveolar collapse, facilitating exit of small water molecules. This would explain the relationship present in Fig. 4 where these patients with the largest estimated right-to-left shunt (i.e., the most areas of alveolar collapse) had the largest increase in extravascular lung water volume with the high mixture of inspired oxygen.

Conclusion

We conclude that the administration of high oxygen mixtures has no adverse hemodynamic effect in patients with uncomplicated acute myocardial infarctions. More work is required in those with acutely compromised left ventricular function.

Extravascular lung water space is frequently increased with apparently uncomplicated infarction, most likely due to transient increases in pulmonary venous pressure which may occur very early in the process. Further increases in accessible lung water volume occur with increased inspired oxygen mixtures, probably related to alterations in capillary permeability in the areas of micro-atelectasis.

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Venous delay: a major source of error in isotopic cardiac output determination

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Serial hemodynamic studies are opening new avenues in our understanding of circulatory adjustments and response to therapy but their performance in man obviously requires a dependable non-invasive technique. It has been previously reported that cardiac output determinations based on radionuclide dilution are as accurate as the standard, more invasive method. Correlation coefficients as high as 0.95 were reported between cardiac output determined from precordial counting and the values obtained from dye dilution curves and arterial sampling. However preliminary studies in our laboratory and reports from others[1] showed that such high correlations were not always attainable in clinical practice. There were no apparent technical reasons for this discrepancy; however we noted in some patients a delayed circulation of the radioactive bolus at the level of the subclavian vein. The possible influence of this venous delay on the accuracy of cardiac output determination has not, to our knowledge, been critically assessed; therefore, simultaneous output determinations by dye (indocyanine green) dilution and by precordial counting (scintillation camera) were compared in 28 patients who had no obvious technical reason of error related to either injection technique, camera positioning, or curve extrapolation.

Material and methods

Thirty studies were carried out on 28 patients to compare the results of cardiac output obtained with ^{99m}Tc labeled HSA with those obtained simultaneously using cardiogreen dye.

Patients. All 28 patients were drawn from the population followed in the Research Division of the Cleveland Clinic. Most were hypertensive with varying degrees of blood pressure control. Their ages varied from 18 to 68 years, and the group included 10 women and 18 men. To all the details of the study, the hazards of arterial puncture and the radiation dose involved were explained and from all a written informed consent was obtained. Two patients had two consecutive studies at the same sitting.

Blood volume and indocyanine green hemodynamic study. All studies were performed in the morning after an overnight fast. After a resting period of at least 30 minutes and positioning of catheters, patients had plasma volume determined by intravenous injection of ^{131}I RISA and blood sampling 10 minutes after the injection. Blood volume was then calculated from plasma volume and simultaneously determined hematocrit. Cardiac output was determined in triplicate using indocyanine green dye (5 mg.) introduced into a right atrial catheter and then flushed into the circulation in less than a half second with 5 ml. saline. Blood was withdrawn from the arterial catheter positioned under fluoroscopy in the root of the ascending aorta. Arterial blood withdrawal was done through a Gilford densitometer using a

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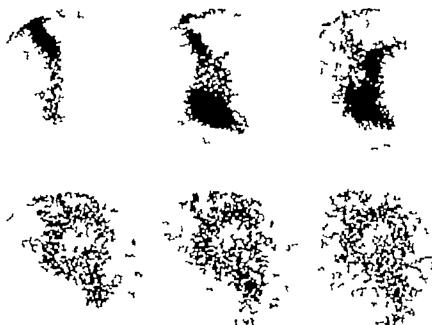


Fig. 1 Information collected at one second interval during the first passage of the radionuclide tracer through the heart (LAO position). *Upper panel.* Arrival of 99mTc-HSA bolus into superior vena cava, right ventricle, and pulmonary artery. *Lower panel.* Same study showing arrival of bolus into left heart and aortic arch. Note no persistence of radioactivity in the subclavian vein area. Time elapsed between upper and lower panels—3 seconds.

constant rate pump with the speed set between 0.3 and 0.5 ml./sec. Curves were inscribed on a fast response recorder and blood was reinfused immediately after the curve inscription thereby ensuring no blood loss during investigation. A [fo]urth dye dilution curve was then obtained by [th]e same method simultaneously with the isotope dilution study—the dye being injected into the right atrium via the appropriate catheter while the radioisotope was delivered as a rapid bolus through a peripheral vein in the other arm as described below. The two patients who had two radionuclide studies during their hemodynamic evaluation had a fifth dye dilution curve obtained simultaneously with the second isotope dilution study. Proper calibration of the dye system was done at the end of each study using known dye concentrations at the same pump speed used during output determinations.

Radionuclide dilution curves.

Instruments. A portable Ohio Nuclear scintillation camera with a medium sensitivity low energy collimator was used for precordial recording of the radioactivity passage. A camera head was tilted to a left oblique position at 30 to 45 degrees parallel to the longitudinal body axis and 0 to 5 degrees upward in the coronal plane to help visualization of the subclavian veins. The camera output was transferred to an Ohio Nuclear 150 Datastore with individual frames being stored on magnetic tape. Recording, storing, and playing back functions were effected by an offline PDP 15.

Various size areas of interest were defined in the areas of the right (RV) and left ventricle (LV) delineated on the original computer printout as previously described[7] the counts from these areas were then played back diagrammatically as time-activity curves. The areas under the curve were calculated by computer integration and least squares fitting of the trailing edge.

Isotope. 99mTechnetium labeled human serum albumin (99mTc HSA) prepared by a unit dose reagent kit* was used with 0.7 mg. HSA mixed with 5 to 20 mCi 99mTc by manual shaking for 10 seconds. The preparation was then ready for use after 20 minutes. The stability of the bond between 99mTc and HSA was tested in two ways. The first method consisted in running a known amount of the preparation through a column of Sephadex gel (G25 coarse) and counting the gamma activity within the albumin peak. Samples tested in this way were obtained under the following conditions: (1) A sample was run

*Union Carbide, Tuxedo, N. Y.

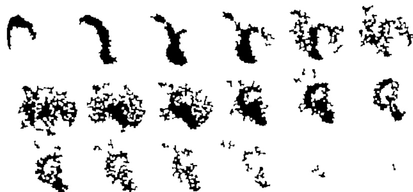


Fig. 2. Delay to the right entricle. Sequential view taken at one second interval, by the time radionuclide activity was maximum in the right ventricle, some radioactivity was still detected in the region of the right subclavian ein (4 mCi 99mT HSA injected via right basilic vein). This had completely disappeared by the eighth second when the radionuclide bolus had started t show in the left entricle.

immediately as soon as the preparation was ready for use then another equal sample of the same preparation was run 30 minutes later through same column. The initial sample showed 97 per cent ± 0.87 (SD) of radioactivity bound to albumin this percentage dropped only to 96 per cent ± 1.31 ($p > 0.20$) in the 30 minute sample. (2) In another approach the 99mTc HSA preparation was injected into normal volunteers and the amount of radioactive material bound to albumin was determined in the preparation after injection, *and in plasma samples drawn 10 minutes and 30* minutes after intravenous injection. The percentages were 95% ± 1.28, 94% ± 1.28, and 92% ± 3.14, respectively (p for difference from control >0.20 and >0.05, respectively)

The second method did not involve blood sampling but involved the part of the cardiac output study concerned with the recording of the final dilution. This showed a plateau with no appreciable slope (0.86 per cent/minute or 4.33 per cent/5 minute, range 3.04 to 5 78) this steadiness of the counts was related to the stability of the 99mTc HSA bond for that period of time.[16]

Procedure. A bolus of 8 to 12 mCi 99mTc HSA was used in the case of a single output determination. *In the event of two output determinations in* the same sitting, a dose of 4 mCi was used for the first study and 8 mCi for the second. A background frame of 60 seconds duration was obtained prior to the second injection. The counts during this second study were then corrected for the background. Whole body radiation dose originating from one millicurie was calculated to be less than 0.018 rad.

The bolus was flushed with 20 ml. normal saline in 3 seconds. During the following 30 seconds, 60 frames were collected for 0.5 second periods on the Datastore and stored sequentially on the magnetic tape. An additional 20 frames were then collected for 30 seconds each (total of 10 minutes) and were stored on the tape for calculation of final dilution. A computer program was written for printing the figures pertaining to each period of count collection during the bolus passage. The figures were plotted on semilog *paper for determination of the downslope of the* curve.

Calculations. Cardiac output was calculated from Hamilton formula[11]

$$F = \frac{I}{\int^{\infty} c\,dt}$$

In the case of dye (indocyanine green) I is the amount of indicator injected in mg. In the case of 99mTc-cardiac output, calculations were made as previously described in detail I being equal to the product of the volume of dilution (blood volume in ml. as measured 10 minutes post RISA injection) by the counts recorded 10 minutes after injection of 99mTc HSA (final dilution) Cardiac output was calculated separately for the right and left ventricles (RVCO and LVCO respectively) the the average (RVCO + LVCO)/2 was derived.

It was observed that in some patients the bolus of radioactive material had various degrees of delay (persistence of radioactivity) in the region of the subclavian vein. Therefore, patients (or

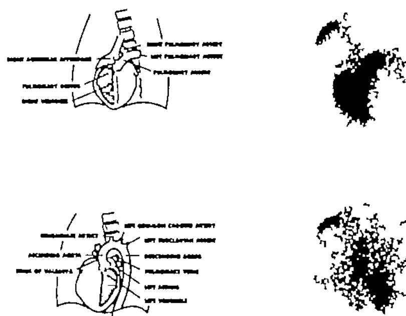


Fig. 4. Delay to the left ventricle. Radioactivity persisting in the region of the subclavian vein when counts were maximum in right ventricle *(upper view)* and in left ventricle *(lower view)* time elapsed between the 2 views was 8 seconds. The two diagrams represent the relative anatomical relationships of the cardiac chambers and big vessels in left anterior oblique position. The shaded areas represent the right ventricle *(upper diagram)* and left ventricle *(lower diagram)*.

studies) were grouped according to the extent of venous delay into four categories.

1. No delay when no radioactivity was ~~e~~cted into the anatomical location of the ~~sub~~clavian vein at the time the maximum count was attained into the right ventricular area (Fig. 1)

2. Mild delay when a radioactivity of 50 per cent of the maximum counts was detected into the region of subclavian vein at the time the counting rate over the right ventricle was maximum (Fig. 2)

3. Moderate delay when a radioactivity of 80 per cent of maximum counts in the frame was detected in the subclavian vein area when counts in the right ventricular area were maximum (Fig. 3)

4 Severe delay when radioactivity of any amount still persisted in the region of subclavian vein at the time the left ventricular counts were maximum (Fig. 4)

However analysis of results showed no difference in findings between delays confined to RV whether mild or moderate Therefore the 30 studies were regrouped into the following categories. Group I (no delay)—including 7 studies, Group II (delay to RV)—including 17 studies Group III (delay to LV)—including 6 studies.

Statistical analysis. Data were analyzed as follows (1) correlation for dye dilution curves between the average for the three initial curves (DD) and the output determined simultaneously with ^{99m}Tc HSA (DD Tcm) (2) Correlation between the last dye-dilution (DDTcm) and the radionuclide cardiac output determined from right ventricular curves (RVCO) from left ventricular curves (LVCO) and as the average of the two. (3) Correlation between radionuclide RV output and LV output. These correlations were studied first in all patients as a single group, then correlations were calculated for studies grouped according to the extent of venous delay Two patients had two consecutive studies at the same sitting in one of the two studies, there occurred a marked venous delay The correlations reported for the 28 patients as a group were calculated on the basis of one study (whichever happened to be first) per patient. However in correlations of subgroups based on the presence and degree of delay each study was included in its appropriate subgroup.

Results

The repeatability of the dye dilution method during the test was studied by comparing the output value obtained simultaneously with the

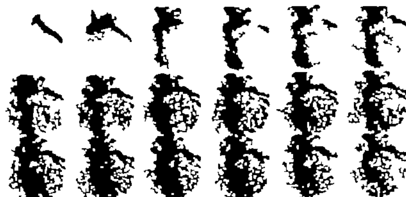


Fig. 4. Sequential views at one second interval obtained after intravenous injection of 4 mCi bolus of 99mTc HSA through the left basilic vein. Not only was there prolonged persistence of radioactivity in the subclavian region, but also reflux into the jugular system.

Table I. Correlation (r) between output values obtained from simultaneous isotopic and dye dilution curves (Studies in 28 patients, one study/patient)

	DD vs RVCO	DD vs LVCO	DD vs (RVCO+LVCO)/2	RVCO vs LVCO
r	0.76	0.82	0.81	0.90
p	<0.001	<0.001	<0.001	<0.001
r^2	58%	67%	66%	81%
slope	0.91	0.95	0.93	0.88
intercept	0.94	0.22	0.58	0.25

Abbreviations: DD = dye dilution cardiac output, RVCO = radionuclide output from right ventricular curve, LVCO = radionuclide output from left ventricular curve; r^2 = index of determination; p = significance of the correlation coefficient.

Table II. Correlation (r) between output values obtained from simultaneous isotopic and dye dilution curves (7 studies with no venous delay)

	DD vs RVCO	DD vs LVCO	DD vs (RVCO+LVCO)/2	RVCO LVCO
	0.87	0.90	0.90	0.95
p	<0.001	<0.001	<0.001	<0.001
r^2	76%	81%	81%	91%
slope	0.70	0.78	0.73	0.99
intercept	1.96	1.42	1.68	0.19

Abbreviations as in Table I.

radionuclide output to the average of 3 dye dilution outputs obtained immediately before the radionuclide injection. The correlation coefficient for 28 patients was 0.96. For the 28 patients as a group, cardiac output values calculated from indocyanine green dye showed fair agreement with the values obtained from precordial counting; the correlation coefficient varied from 0.76 to 0.82 depending on the area selected (Table I).

The observation of venous delay in some of these patients allowed their separation into the three groups described above. The correlation between dye dilution output and the average radionuclide output (RVCO + LVCO)/2 in patients without delay (r = 0.90) (Table II) was comparable to the correlation coefficient obtained by Alazraki and colleagues. Similar r values (r = 0.90) were obtained in the presence of persistence of radioactivity into the subclavian veins at the time of maximum right ventricular counts (Group II Table III). In contrast the r value fell to 0.64 (index of determination 41 per cent) in patients showing severe venous delay (delay to LV Table IV).

The total occurrence of venous delay appeared more frequently when the injection was performed in the left arm (89 per cent vs 63 per cent in those who had the injection into the right arm). However the difference was not significant χ^2 = 3.48, p ns). Moreover the percentage of severe delay was not significantly different whether the injection was right or left sided (12.5 per cent vs 22 per cent, χ^2 = 1.25 p ns). An unusual feature was observed in two patients who were injected in the left arm a reflux of the material occurred into the jugular system (Fig. 4) and the delay in arrival of radioactivity was such that the cardiac output curves were unreadable. These two patients were not included in the correlation reported above because they did not have simultaneous dye dilution studies.

Table III Correlation (r) between output values obtained from simultaneous isotopic and dye dilution curves (17 studies with delay to RV)

	DD vs RVCO	*DD vs LVCO*	*DD vs (RVCO+LVCO)/2*	*RVCO vs LVCO*
	0.68	0.88	0.90	0.93
p	<0.001	<0.001	<0.001	<0.001
r^2	75%	77%	81%	86%
slope	0.96	1.09	1.02	1.06
intercept	0.71	−0.35	0.19	−0.67

Abbreviations as in Table I.

Table IV Correlation (r) between output values obtained from simultaneous isotopic and dye dilution curves (6 studies with delay to LV)

	DD vs RVCO	*DD LVCO*	*DD vs (RVCO+LVCO)/2*	*RVCO vs LVCO*
r	0.59	0.71	0.64	0.96
p	>0.1	>0.1	>0.1	<0.01
r^2	35%	50%	41%	92%
slope	0.88	0.69	0.79	0.83
intercept	0.97	0.96	0.96	1.09

Abbreviations as in Table I.

The frequent occurrence of venous delay (severe in 20 per cent of this series) was confirmed in a subsequent study of another 63 radionuclide output determinations. In these, severe delays occurred in 16 per cent while mild and moderate delay occurred in 59 per cent. These results underline the importance of use of the scintillation camera and adequate countings of subclavian regions.

The relationship between the extent of venous delay and the speed of circulation was analyzed in 29 studies selected from our whole population because of definite evidence of fast or slow circu The first group included 18 studies done in with the diagnosis of hyperbeta-adrenergic state or arteriovenous fistula or receiving intravenous isoproterenol infusion. The second group included 11 studies done in patients receiving beta blockers or venodilators. The percentage occurrence of no mild, and moderate venous delay in the two groups was 44 per cent, 44 per cent, and 11 per cent in the presence of hyperkinetic circulation and 9 per cent, 45 per cent, and 45 per cent in the presence of slow circulation. None of the studies in this group had severe venous delay In general, in studies showing severe venous delay no common factor could be defined, in 16 such studies from our total population (including six reported in this series), cardiac output was less than 4 L./minute in 19 per cent and above 6 L./minute in 44 per cent total blood volume was ≤90 per cent of normal for our laboratory in 19 per cent and ≥110 per cent in 31 per cent patients were under arious medications and their clinical signs aried widely Moreover hyperlipidemia was present in tw only hypertensive heart disease in two anemia in one, and chronic obstructive lung disease in n

Discussion

Cardiac output determination by precordial counting depends on the rapid delivery of a concentrated bolus of radionuclide to the area of interest. Delay of radioactive material in the subclavian venous system was described by Berner and associates[10] Oldendorf and colleagues,[13] Ashburn, and Lane and co-workers described methods of rapid bolus delivery with intravenous injection. However despite the use of a rapid flush technique, persistence of radioactivity in the region of subclavian vein was encountered in 77 per cent of our studies. This incidence was confirmed in a subsequent review of the next 63 radionuclide cardiac output studies; some delay was recognized in 47 studies (75 per cent). However delays differ in magnitude; mild to moderate delays are most frequent (59 per cent), whereas severe delays occurred in only 16 per cent. Not only was a venous delay observed in these patients, but in two instances, actual reflux of the injected material into the jugular system was seen both had been injected into the left basilic vein (Fig. 4)

The effect of venous delay on accuracy of cardiac output determination has not been reported. In order to evaluate that influence, we have used a classification of venous delay based on the relation between the persistence of radioactivity in the subclavian vein region and the maximum counts in the right and left ventricular areas. The correlation coefficient between dye dilution output and radionuclide dilution output (RVCO + LVCO)/2 fell from 0.90 in those who had either no delay" or only "delay to RV" to 0.64 in those having "delay to LV" (Table IV). Therefore, the recognition of a venous delay per se did not allow accurate separation of acceptable

from unacceptable studies. Some quantification such as the one described here is needed. This is particularly important because in all three groups (*no mild, and severe delay*) *the right ventricular* radionuclide output correlated with the left ventricular output with an r value above 0.90 ($p < 0.01$) *Thus, similarity between RVCO and* LVCO cannot be taken as an internal standard for an acceptable output value.

The reason for the delay specially in its severe form, is not clear. It did not seem to be related to the speed of circulation. Although the percentage occurrence of no mild, and moderate delay in a group of patients with clinical and hemodynamic evidence of hyperkinetic circulation was 44 per cent, 44 per cent, and 11 per cent, respectively as opposed to a percentage of 9 per cent, 45 per cent and 46 per cent in a group with slow circulation, no definite relation to the speed of circulation was found in studies with severe delay Venous delay did not seem related to venous obstruction because of absence of any suggestive history or physical signs in our patients. Also a simultaneous bilateral mediastinal venogram done in a patient who showed marked delay with reflux of radioactive material from the subclavian into the *jugular system did not show evidence of venous* occlusion, stenosis, or kinking at any site from injection point to the right atrium. The incidence *of delay could not be related to the speed of* injection since the same speed, and the same amount of flush were used in all patients. It could not be attributed to anatomical variations in relation to the long course of the left innominate vein because the incidence of severe delay was not statistically different between those patients injected in the right arm and those injected in the left side. Finally the physical characteristics of the injectate could not be responsible it is not olly per se and the albumin content of 1 ml. ^{99m}Tc HSA could not be reasonably expected to change blood viscosity

Summary

The high correlation reported for cardiac output determinations by ^{99m}Tc HSA has not held for other unselected series. To investigate possible causes, cardiac output was determined simultaneously by two indicators. ^{99m}Tc HSA and indocyanine green both injected by rapid flush technique, the ^{99m}Tc via antecubital vein and the dye (DD) via superior vena cava. Precordial counting rates were obtained by scintillation camera and dilution curves were derived by computer program from selected areas in right (RV) and left ventricles (LV). Thirty consecutive studies showed significant ($p < 0.001$) correlation ($r = 0.81$) between ^{99m}Tc and DD output but a determination index of only 66 per cent. Varying *degrees of persistence of counting* rate were noted in the subclavian region in the absence of demonstrable venous obstruction. In seven studies (Group I) *there was no isotope hang up in the* subclavian region In 17 (Group II) counts in the subclavian region persisted only through RV visualization, and in six studies (Group *III*) counts persisted even when radioactivity was at its peak concentration over LV Correlation coefficients (*^{99m}Tc output with DD output*) *varied* inversely with delay r was 0.90 for Group I and Group II, and 0.64 for Group III (determination indices 81 per cent, 81 per cent, and 41 per cent, respectively).

Results suggest that unexpected delay in arrival of radioactive bolus into the heart results in erratic distortion of cardiac output values. Unless monitored, delay often remains unsuspected in a consecutive series of 63 ^{99m}Tc studies severe delay occurred in 16 per cent

The reason for the delay is not clear It did not seem related to the speed of circulation to the presence of venous obstruction, or to anatomical variations. *It could not be related to the speed of* injection or to the physical characteristics of the injectate.

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Total and regional myocardial blood flow in aortic regurgitation

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The mechanism of angina pectoris in patients with aortic valve disease and aortic regurgitation, in particular is a subject of great interest. It is suspected that these patients may have inadequate coronary flow in the presence of normal coronary arteries. Studies on the femoral, brachial, and subclavian arteries of patients with aortic regurgitation have shown considerable retrograde flow. These studies have been confirmed in dogs. Experimental studies in dogs with mechanically induced aortic regurgitation have demonstrated reverse diastolic coronary flow. This has also been documented in patients using coronary electromagnetic flow probes at surgery. Coronary angiographic studies have demonstrated abnormal phasic coronary flow in patients with aortic valve disease. Although it is known[4-6] that phasic coronary blood flow in the epicardial arteries shifts from diastole to systole in the presence of acute aortic regurgitation, controversy still exists whether there are compensatory regional coronary flow changes which maintain adequate blood flow to the myocardium. The purpose of this study was to investigate total and regional myocardial blood flow and see if they were related to the degree of induced aortic regurgitation in acute, open-chest dogs.

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Methods

Studies were made on 12 dogs weighing 24.1 kilograms ± 3.01 SD. They were anesthetized with sodium pentobarbital, 34 mg./Kg. intravenously. The tracheas were intubated, and the dogs were ventilated with room air and oxygen using a Harvard respiratory pump. Arterial blood samples were monitored to maintain pH between 7.3 and 7.4, pCO_2 between 35 and 40 mm. Hg, and pO_2 greater than 90 mm. Hg. The right femoral artery and vein, as well as the right brachial artery were isolated and catheterized. A midsternal thoracotomy was performed, and the heart was suspended by a pericardial cradle. A cannula was placed in the left atrial appendage, and a 6.5 mm. high fidelity transducer (Konigsberg) was placed into the left ventricle via the left atrial incision. Left ventricular pressure and Vmax[14] were determined from the high fidelity left ventricular pressure tracings. Aortic pressure was also measured with a high fidelity transducer. An electromagnetic flow probe (2 to 3 mm.) was placed on the proximal portion of the left anterior descending artery. A 14 to 18 mm. electromagnetic flow probe was placed on the ascending aorta approximately 4 cm. above the aortic valve. A Statham Model SP2201 Autoranging Blood Flowmeter with non-occlusive zero function was used to obtain simultaneous aortic and coronary flow measurements. Electrocardiogram and pressure signals were recorded on a Brush-Gould Multi-Channel Recorder as well as a Hewlett Packard 3960 FM tape system for later playback and analysis. Pressure analysis was done by hand calculation as well as on a PDP 11/35 computer.

The subclavian artery was exposed just above

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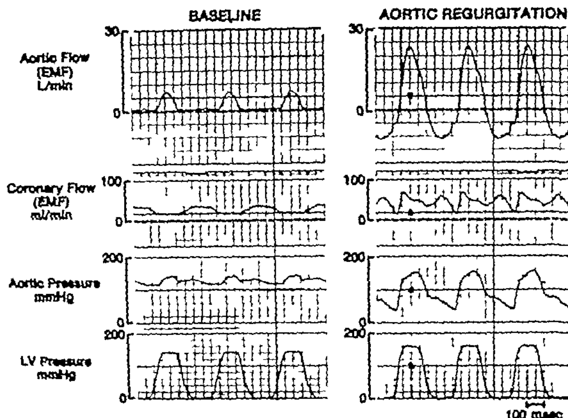


Fig 2 Tracing showing aortic blood flow and coronary blood flow during control conditions and after induction of aortic regurgitation. The amount of aortic regurgitation (53 per cent) is quantitated by planimetrizing the areas above and below the zero flow line as indicated in the text. There is marked increase in systolic coronary blood flow and diastolic blood flow remains the same (D/S = 0 76).

determined by planimetry of the phasic coronary flow record for five cardiac cycles. A ratio of diastolic coronary blood flow to systolic coronary blood flow was determined as described by Folts and Rowe.

Simultaneous pressure recordings from the left ventricle and aorta were used to estimate the ratio of subendocardial coronary blood flow to the left ventricular oxygen requirements, as previously reported by Vincent and co-workers. According to this method, potential subendocardial perfusion is estimated by using a diastolic pressure time index (DPTI) obtained by planimetry of the area between the superimposed aortic and left ventricular pressure curves in diastole. Myocardial oxygen requirements are estimated from a modified tension-time index, obtained by planimetry of the area beneath the left ventricular pressure curve from the onset of ventricular systole to closure of the aortic valve represented by the dicrotic notch on the aortic pressure tracing. If the dicrotic notch was not apparent, we then chose the point at which aortic flow fell below zero as the time of aortic valve closure. Since this is a pressure measurement rather than a tension measurement, it is termed the systolic pressure-time index (SPTI) The ratio DPTI SPTI is used as an estimate of the inadequacy of left ventricular subendocardial blood flow

Myocardial perfusion was measured with 7 to 9μ microspheres labeled with [illegible]Sr [illegible]Ce, [illegible]Sc and [illegible]Nb. This technique has been described by this laboratory in detail elsewhere[illegible] and is only briefly summarized below For each flow measurement, between 1.76×10^{4} to 4.67×10^{7} microspheres were suspended in 0.1 to 1.9 ml. of 10 per cent dextran and injected into the left atrium. Prior to injection, the vial containing the microspheres and Tween-80 was vigorously agitated mechanically for at least three minutes. Microscopic examination of each new bottle of microspheres dispersed in the manner described above showed

Table I Hemodynamic variables of 12 dogs with aortic regurgitation Mean control values and mean raw change from baseline during aortic regurgitation

	Control	Aortic regurgitation		
		Mild (0-25%)	Moderate (25-50%)	Severe (50-80%)
Heart rate (beats/min)	163.42 ± 20.09	−5.00 ± 9.99	−4.92* ± 6.65	−6.56 ± 9.00
LV SYS (mm. Hg)	126.58 ± 21.99	0.40 ± 11.37	2.50 ± 11.39	6.44 ± 11.80
LV DIAS (mm. Hg)	4.80 ± 2.39	0.00 ± 1.70	0.00 ± 2.26	1.67 ± 2.00
Aortic SYS (mm. Hg)	128.67 ± 22.17	−2.10 ± 12.44	−2.64 ± 11.96	−3.78 ± 10.34
Aortic DIAS (mm. Hg)	101.00 ± 21.66	−8.80 ± 11.65	−19.64 ± 14.84	−40.33* ± 20.40
DPTI/SPTI	1.18 ± 0.17	−0.12* ± 0.11	−0.24 ± 0.12	−0.56* ± 0.22
Vmax (28.8 × length, sec.)	68.98 ± 12.92	7.82* ± 6.45	16.69* ± 12.26	26.82* ± 13.47
Aortic flow (L./min.)	1.60 ± 0.70	0.07 ± 0.30	−0.20 ± 0.42	−0.23 ± 0.55
LAD flow (ml./min.)	30.34 ± 14.18	3.91 ± 6.60	4.43 ± 5.62	10.20* ± 8.63
DIAS/SYS ratio	4.22 ± 2.02	−0.28 ± 2.33	−1.44 ± 1.62	−3.31 ± 2.31
DIAS LAD flow (ml./min.)	23.92 ± 11.35	2.78 ± 4.83	1.17 ± 4.06	−3.15 ± 6.04
SYS LAD flow (ml./min.)	6.41 ± 3.45	1.17 ± 2.91	3.26* ± 2.48	12.36* ± 6.97
MYO flow (ml./100 g./min.)	99.90 ± 34.22	−5.63 ± 20.30	11.18 ± 26.45	21.63 ± 22.28
Endocardium (ml./100 g./min.)	97.27 ± 30.73	−6.26 ± 20.96	10.26 ± 36.71	7.39 ± 25.57
Epicardium (ml./100 g./min.)	100.16 ± 37.25	−7.28 ± 20.63	7.68 ± 33.28	21.58 ± 23.08
ENDO/EPI ratio	0.98 ± 0.11	0.01 ± 0.07	0.01 ± 0.06	−0.11 ± 0.18

*Denotes significant change from baseline state ($p < 0.05$).

Abbreviations: LV SYS = left ventricular systolic pressure; LV DIAS = left ventricular diastolic pressure; Vmax = contractile element velocity at zero load; DPTI/SPTI = diastolic pressure time index divided by systolic time index; ENDO/EPI ratio = ratio of endocardial coronary blood flow to epicardial coronary blood flow; DIAS/SYS ratio = ratio of diastolic coronary blood flow to systolic coronary blood flow.

that in excess of 98 per cent of the spheres were completely dispersed. Occasionally small groups of three to five spheres were observed. Starting 30 seconds before injection and continuing until three minutes after injection, blood was withdrawn simultaneously from the right brachial and right femoral arteries at 2.06 ml. per minute with a Harvard pump.

Following this study the animals were killed with an injection of potassium chloride. The heart was excised and the free walls of the right atrium, right ventricle, left atrium, great vessels, valves, surface vessels, and epicardial fat were removed. Utilizing the posterior descending coronary artery as a starting point the left ventricle was divided into four equal slices of eight segments each, and each segment was divided into three layers: endocardium, mid wall, and epicardium of approximately equal thickness. Thus, the left ventricle was divided into 96 segments, and the relative geometric position of each segment was constant from animal to animal. Subsequently the myocardial segments were weighed (to the nearest mg.) placed in glass tubes, and counted for five minutes each in three inch well type sodium iodide gamma counter. The average weight of the segments was 1.02 ± SD 0.18 gms.

The reference blood samples were divided into aliquots, making their counting geometry similar to that of the myocardial samples. Energy windows utilized were ^{46}Sc 700 to 1500 keV, ^{85}Sr 400 to 600 keV, ^{95}Nb 650 to 800 keV and ^{141}Ce 125 to 175 keV. Isotope separation was performed utilizing standard techniques.

The myocardial blood flow was calculated using the following formula: $MBF = Cm \times 100 \times RBF + CR$, where MBF = myocardial blood flow in c.c./100 gm. per minute, Cm = counts per gram of myocardium, RBF = reference blood flow (rate of withdrawal from reference arteries), and CR = total counts in the reference blood. The counts in the femoral and brachial blood samples were averaged. The number of spheres present in the brachial and femoral reference samples was rarely identical. The average difference between simultaneous paired reference samples was 3.74 ± 3.42 per cent (mean ± SD). Thus, of the 12 animals studied and 47 flows measured, one flow had a greater than 17 per cent difference between any pair of reference samples and was deleted.

The counts per minute sample weight, and geometric reference number of each segment were punched on computer paper tape. Subsequent

Table II Mean perfusion of major subgroups during baseline, mild (5-25%), moderate (25-50%) and severe (50-80%) aortic regurgitation

Levels	*A*	*B*	*C*	*D*
Base	104.34 ± 5.54	96.14 ± 4.00	96.34 ± 3.40	106.73 ± 6.93
Mild	106.41 ± 6.45	96.14 ± 4.56	93.83 ± 2.50	107.80 ± 13.4
Mod	106.93 ± 5.44	96.30 ± 5.07	94.67 ± 4.06	103.11 ± 8.38
Sev	106.12 ± 3.40	97.37 ± 3.38	95.00 ± 2.90	102.34 ± 3.92
Layers	EPI	MID	ENDO	
Base	99.44 ± 5.87	102.00 ± 3.03	98.27 ± 5.30	
Mild	97.44 ± 4.83	104.07 ± 3.39	98.42 ± 4.73	
Mod	97.37 ± 6.19	106.09 ± 4.23	97.37 ± 7.02	
Sev	101.36 ± 5.15	109.97 ± 5.49	86.96 ± 11.6*	
Walls	POST	SEPT	ANT	LAT
Base	98.39 ± 3.37	100.04 ± 3.64	101.64 ± 3.63	100.01 ± 3.82
Mild	100.83 ± 4.45	96.78 ± 2.92	99.96 ± 4.01	100.55 ± 3.44
Mod	98.65 ± 3.69	96.08 ± 3.06	101.18 ± 3.34	102.00 ± 4.54
Sev	*100.89 ± 4.39*	*97.04 ± 3.42**	*101.45 ± 4.70*	*100.73 ± 3.18*

The left ventricle was divided into four levels (A to D) from base to apex. Each level was divided into eight subsections (two each from anterior, lateral, septal and posterior walls). *Each subsection was divided into three layers (epicardium, mid-wall, and endocardium). Each individual segment was* assigned a geometric reference number (1 to 96) so the similar segments could be compared from study to study. Normalized flow to the major subgroups in per cent are obtained by dividing the absolute flow to that subgroup by the mean flow of all 96 segments.
Abbreviations: Epi = epicardium, Mid = mid-wall; Endo = endocardium, Post = posterior; Sept = septum; Ant = anterior; Lat = lateral.
*Indicates that significant change from the baseline state occurred ($P = 0.05$).

analysis was performed with a PDP 11/35 computer. Individual sample counts greater than 3.5 standard deviations above the mean were deleted to eliminate clumping. This resulted in less than one segment per animal being discarded. Standard statistical techniques (paired t test which gives mean, standard deviations, Student t distribution and one-way Anova) were utilized to analyze the data. All results are expressed as the mean ± 1 standard deviation.

Results

Fig. 2 shows aortic blood flow, left anterior descending coronary blood flow, aortic pressure, and left ventricular pressure under control conditions. The coronary flow tracing demonstrates the phasic nature of coronary flow and, in particular, that the majority of flow occurs during diastole. In contrast, forward aortic flow occurs almost exclusively during systole. Fig. 2 also demonstrates aortic and coronary blood flow after the induction of aortic regurgitation. In this case there is approximately 58 per cent aortic regurgitation, as determined from the aortic electromagnetic flow tracing. With the induction of aortic regurgitation, there is a change in the phasic flow in the proximal LAD artery. Systolic flow increases and diastolic flow decreases. There were no significant changes in total coronary flow in contrast to large changes in the DPTI/SPTI ratio and phasic coronary flow ratio.

Table I is a summary of the mean control values and mean raw changes of measured variables during the induction of aortic regurgitation. The data in this table was analyzed with a standard statistical paired t test.

There are no significant changes in heart rate or left ventricular systolic pressure under mild, moderate, and severe aortic regurgitation. Contractile state, as measured by Vmax, increases significantly with regurgitation. As expected, the aortic diastolic pressure decreases significantly with the induction of severe aortic regurgitation. Total coronary flow as measured by the radioisotope technique, shows no significant change from control to severe aortic regurgitation. There is a decrease in the endocardial/epicardial ratio which is not statistically significant. For moderate and severe regurgitation, there are significant changes in the diastolic/systolic ratios and in the DPTI/SPTI ratios.

Table II shows the of flow

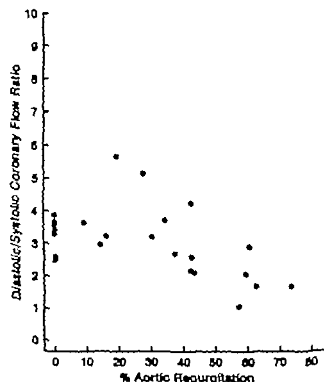


Fig. 3. Plot of coronary diastolic/systolic blood flow ratio versus per cent aortic regurgitation. There is variation in the diastolic/systolic coronary flow ratio in the baseline condition for the 12 animals studied (11 with zero regurgitation and one with 4 per cent aortic regurgitation). As the ratio decreases than one) the majority of flow occurs during systole.

line, mild, moderate and severe aortic regurgitation. As can be seen, there are only small changes in the major subgroups. The largest change is a decrease in the per cent of normalized flow to the endocardium during severe aortic regurgitation. This results in an insignificant change in the ENDO/EPI ratio (see Table I).

Fig. 3 is a plot of the diastolic/systolic coronary blood flow ratio versus the per cent of aortic regurgitation. As can be seen, as the per cent of aortic regurgitation increases, the ratio decreases (r = −0.60). There is a significant increase of systolic blood flow with diastolic flow remaining unchanged (see Table I).

Fig. 4 is a plot of the ENDO/EPI ratio versus the per cent of aortic regurgitation. As the degree of aortic regurgitation increases, there is little change. Statistical analysis shows no direct linear correlation (r = −0.28).

Fig. 5 is a plot of phasic coronary blood flow versus ENDO/EPI ratios. There is no direct correlation (r = .37).

Fig. 6 is a plot of the DPTI/SPTI ratio versus the ENDO/EPI ratio. As published by other authors,[6-] it is assumed that DPTI/SPTI ratio of less than 0.7 is associated with an abnormal ENDO/EPI ratio. As can be seen with increasing abnormalities of the DPTI/SPTI ratio, there is only a weak correlation (r = .36) between the two ratios.

Discussion

Although previous reports[14] failed to demonstrate a significant alteration in coronary blood flow in the presence of aortic regurgitation, more recent studies[6-] have demonstrated consistent changes in coronary artery flow with the production of acute aortic regurgitation. The present investigation, which is an acute study in open-chest dogs, demonstrates the same findings seen in chronic preparations, that systolic coronary blood flow increases and diastolic coronary flow remains the same as aortic regurgitation is increased.

The purpose of the present study was to evaluate the phasic flow relationship and regional myocardial perfusion in aortic regurgitation. In a study of a somewhat similar condition, acute arteriovenous fistula, Buckberg and colleagues[17] reported a decrease in total coronary blood flow with a redistribution of flow in particular an underperfusion of the subendocardial muscle. In both conditions, aortic diastolic pressure falls, but there is no backflow across the aortic valve with an A-V fistula. Also diastolic myocardial stresses may be quite different in the two situations. In the current study there is a marked change in phasic flow from diastole to systole with aortic regurgitation (see Table I). This is noted in Table I and is statistically significant with moderate and severe degrees of aortic regurgitation. Another interesting feature shown in Table I is that, with increasing amounts of aortic regurgitation, total coronary flow remained essentially unchanged. This implies a compensatory mechanism such that, although phasic flow changes from diastole to systole, average flow or bulk flow remains fairly constant. This has previously been shown by Griggs and Chen.[14] An important question is whether there is a change in spatial distribution of flow while total flow remains approximately the same. The spatial distribution of flow with various degrees of aortic regurgitation is shown in Table II. There are no significant changes to major subgroups. However there is a

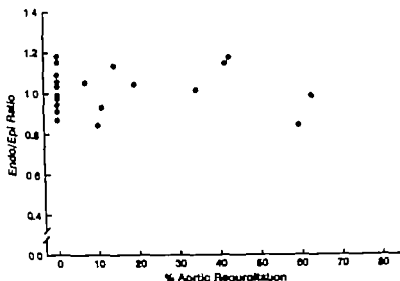


Fig. 4. Plot of coronary ENDO/EPI ratio versus aortic regurgitation. As the degree of aortic regurgitation becomes greater than 50 per cent there is decrease in the endo/epi ratio.

significant decrease in flow to the endocardial layer. The flows to the endocardial and epicardial layers do not cause a statistically significant change in the endocardial/epicardial ratio. As seen in Tables I, II and Fig. 4 there is no linear relationship between distribution of coronary flow and degree of aortic regurgitation. Myocardial metabolic studies done by Griggs and Chen[14] note biochemical signs of anaerobic metabolism of the inner wall of the myocardium only during severe aortic regurgitation. The current study also indicates that, with aortic regurgitation, there are changes in phasic flow in the epicardial vessels, but adaptive mechanisms come into play which tend to preserve the spatial distribution of flow in mild and moderate aortic regurgitation. These mechanisms are inadequate when there is severe aortic regurgitation.

The mechanism by which there is a reduction in diastolic flow and an increase in systolic flow in aortic insufficiency is not clear. Coronary blood flow is related to the driving force, or pressures at the coronary ostia[15] and the resistance of the arterial bed. These resistances consist of: (1) large vessel resistance, (2) intramyocardial stress, and (3) local or terminal resistance. In the present study there is a large change in phasic flow. Because this is a phasic phenomenon, we do not believe it is secondary to small vessel resistance which is thought to be controlled by local metabolic regulators. The three factors which then remain are large vessel coronary resistance, the

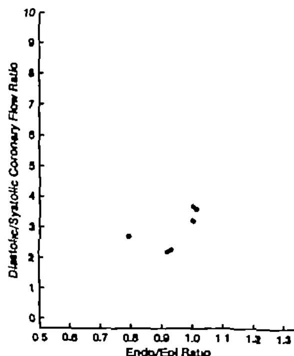


Fig. 5. Plot of coronary diastolic/systolic blood flow ratio versus ENDO/EPI ratios.

driving force at the coronary ostium, and intramyocardial stress. Large vessel coronary resistance is related to the epicardial vessels ability to store flow during one part of the cardiac cycle and maintain intramyocardial flow during the rest of the cardiac cycle. This shift of flow pattern from mainly diastole in the epicardial

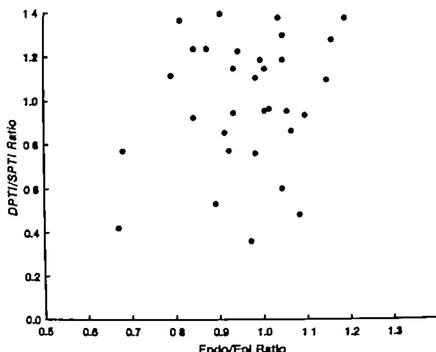


Fig. 6 Plot of DPTI/SPTI versus ENDO/EPI ratios.

vessels to systole in the capillaries has been documented.[19]

In regard to driving force at the coronary ostia, Bellhouse and associates[21, 22] have studied the portance of aortic valve in maintaining a blood in the aortic sinus which positions the aortic cusps such that coronary blood flow can occur These aortic sinus vortices produce the pressure gradient at the coronary orifice. The gradient at the coronary orifice plus the aortic pressure are the driving force for coronary flow The aortic diastolic pressure is decreased in aortic regurgitation. The pressure gradient at the coronary orifice has not been studied. In studies on valves with aortic stenosis,[20] a turbulent jet during ejection has been noted which prevented the normal vortex formation in the aortic sinus and produced an abnormal coronary ostial pressure gradient. It is conceivable that aortic regurgitation can produce faulty movement of the aortic cusps, and there could be a change in the pressure gradient across the coronary ostium secondary to the vortex as well as the decrease in diastolic aortic pressure.

The intramyocardial stress during diastole is directly proportional to the pressure in the ventricle as well as to the shape of the ventricle. With aortic regurgitation, left ventricular diastolic pressure increases, and there is an increase in end-diastolic volume[23] so that the intramyocardial stresses are probably increased, thus causing increased resistance to flow during diastole. The relationship of intramyocardial stresses to coronary flow is not known. However recent studies[?] have documented that there is a transmural gradient of myocardial blood flow when coronary inflow was limited to systole. This resulted in subendocardial underperfusion with subepicardial layers normally perfused.

Summary

Total, phasic, and regional flow were studied in 12 open-chest dogs with aortic regurgitation. An adjustable catheter device was used to produce aortic regurgitation. Four differently labeled 7 to 9μ microspheres were injected into the left atrium during control, mild (5 to 25 per cent) moderate (25 to 50 per cent) and severe (50 to 80 per cent) regurgitation. Aortic regurgitation (AR) and the ratio of diastolic coronary blood flow to systolic coronary blood flow (DIAS/SYS RATIO) were measured from the electromagnetic flow tracings. The simultaneous left ventricular and aortic pressures were used to calculate DPTI/SPTI (diastolic pressure time index to systolic time index). Myocardial flow flow to major subgroups, and

endocardial/epicardial ratios were determined from radioisotope analysis of the left ventricle.

Mean absolute control values and mean changes of key variables from control were

Table III

	Control	Mild AR	Mod AR	Severe AR
Heart rate (beats/min.)	163.42	−5.03	−4.65*	−8.56
DPTI/SPTI	1.18	−0.12*	−0.24	−0.56*
Dias/Sys ratio	4.23	−0.28	−1.64	−3.31
Myo. flow (ml./100 g./min.)	99.90	−5.63	11.18	21.63
Endocardium (ml./100 g./min.)	97.27	−5.28	10.26	7.29
Epicardium (ml./100 g./min.)	100.18	−7.35	7.86	21.65
ENDO/EPI ratio	0.99	0.01	0.01	−0.11

*Denotes significant change from control state ($P < 0.05$)

The phasic coronary blood flow results in this study are similar to those reported in chronic, intact anesthetized dogs; when the degree of aortic regurgitation increased, there was a significant decrease in diastolic coronary blood flow with an increase in systolic coronary blood flow. Not previously reported are the changes in the distribution of myocardial perfusion. Total myocardial flow increased slightly. There were minimal changes in blood flow to the endocardium which resulted in a slight decrease in the ENDO/EPI ratio and a decrease in the per cent of flow to the endocardium. These results indicate that, although acute aortic regurgitation produces significant changes in phasic coronary flow, there are much smaller effects on total and regional myocardial blood flow.

The catheter spreading device used in this study was made by Jim Rogers of Jim's Instrument Manufacturing, Inc., 1660 Oak Lake Rd., Iowa City, Iowa.

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Effect of exercise on left ventricular ejection fraction in men with coronary artery disease

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Coronary arteriography is frequently performed to evaluate the patient suspected of having coronary disease. This procedure, although very specific for the presence of structural coronary disease, is invasive and does not provide direct information about myocardial blood flow Both the symptom of angina and exercise electrocardiography are associated with problems of both specificity and sensitivity in respect to a diagnosis of coronary disease as defined by coronary arteriography

Myocardial ischemia should be associated with n alteration of left ventricular performance. egional left ventricular contraction abnormalities have frequently been observed in patients with coronary disease.[1-4] These abnormalities have been observed in infarcted left ventricular segments, in segments supplied by obstructed coronary arteries, and have been shown to increase in frequency with increasing severity of coronary arteriographic abnormalities. Left ventricular ejection fraction has been found to be frequently depressed in patients who have sustained an acute infarction and ejection fraction has been found to decrease with exercise in patients with coronary disease.[8]

In the present study left ventricular ejection fraction was measured before and during bicycle exercise in normal men and in men with coronary artery disease. Men with and without abnormal resting ejection fraction and men who did and did not develop electrocardiographic changes with exercise were included.

Patients

Exercise testing was undertaken in 46 men (aged 33 to 60 years average age 43 years). These men had all undergone cardiac catheterization with coronary and left ventricular cineangiography within six months of exercise testing. Cardiac catheterization was performed to evaluate chest pain which was either typical or atypical of angina. Thirty-one men had coronary artery disease with at least one area of at least 60 per cent obstruction (per cent luminal diameter) in at least one major coronary artery and 15 men had perfectly normal coronary arteries. None of the men had arterial hypertension or valvular heart disease and none had received any medication except nitroglycerin in the 48 hours prior to exercise testing. None had received digitalis in the three months prior to study All of the men understood the purpose of the study and ga[…] their consent.

Methods

Graded exercise was performed in the supine position with a bicycle ergometer (Quinton Instruments, Seattle, WA) Exercise was discontinued when either definite ST segment depression (≥ 1 mm. horizontal or down-sloping), frequent ventricular premature beats, angina, fatigue, or dyspnea was observed.

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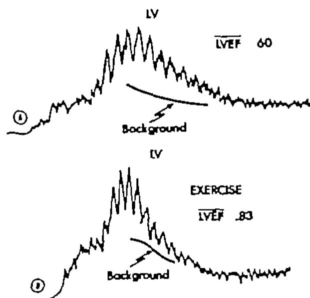


Fig. 1 A and B. Resting time *(horizontal axis)* vs radioactivity *(vertical axis)* curve in a normal man *(A)*. The left ventricular peak *(LV)* and background count rate are identified. Left ventricular ejection fraction *(LVEF)* averaged .60 for the three beats indicated ( ). The ejection fraction on exercise averaged .83 *(B)* for three beats indicated ( ).

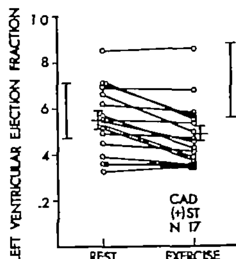


Fig. 2. Individual slopes for rest and exercise left ventricular ejection fraction in 17 men with coronary artery disease (CAD) and ST segment depression (±ST) during exercise. The average ±SEM is indicated, as are the normal ranges.

Left ventricular ejection fraction was measured at rest and just prior to discontinuation of exercise with a dual-crystal scintillation probe (Searle Radiographics, Des Plaines, IL). For this determination about 2 millicuries of ^{99m}Technetium was injected into a venous catheter positioned in the superior vena cava and flushed with saline. The scintillation probe was positioned over the mid point of the left ventricle in supine, anteroposterior projection and following injection of tracer the probe simultaneously recorded a left ventricular time vs radioactivity curve and a left ventricular background curve (Fig. 1).

Left ventricular ejection fraction was calculated as the fractional fall in count rate from end-diastole to end-systole divided by the end diastolic count-rate. The tails of the two curves (left ventricle and background) were matched to obtain the background correction for calculation of end-diastolic count rate (Fig. 1).[11] Ejection fraction was computed for at least three consecutive beats, beginning with the first beat after the peak of the left ventricular time vs activity curve, and averaged. Beat-to-beat variation was always less than 5 per cent.

The dual-crystal scintillation probe accurately measured left ventricular ejection fraction. In another group of 25 men with coronary artery disease left ventricular ejection fraction obtained with the dual crystal probe correlated with contrast left cineventriculograms obtained in the right anterior oblique projection (r = 0.89). Ejection fraction varied from .23 to .86 in these patients.

From the ventriculograms left ventricular volume (V) was computed from the projected end-diastolic and end-systolic areas (A) and the long axis (aortic valve to left ventricular apex) (L)[12] as,

$$V = \pi/6\ LM \quad (1)$$

where M was the left ventricular minor axis, calculated from the projected area and the long axis as,

$$M = \frac{4A}{\pi L} \quad (2).$$

Calculations were performed with the assistance of an X Y digitizer and a digital computer. Beats selected for analysis included only those within the first four after contrast injection. Sinus beats following a premature beat were excluded. Regression equations were not utilized.

Results

In the 15 normal men resting left ventricular ejection fraction averaged .59 ± .06 (±SD). Using two standard deviations from the average to define the normal range, normal resting ejection fraction was .47 to .71. During exercise in the normal men left ventricular ejection fraction averaged .72 ± .08 with a range (±2SD) of .56 to

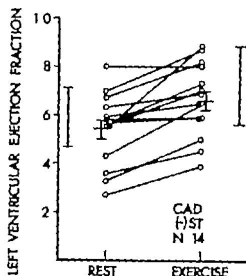


Fig. 3 Individual values for rest and exercise left ventricular ejection fraction in men with coronary disease (CAD) who did not develop ST segment changes during exercise. The normal ranges and the average values ± SEM are shown.

.88. None of the normal men had a resting ejection fraction of less than .53 and an exercise ejection fraction of less than .63 Ejection fraction increased by at least .06 in all normal men.

For the 31 men with coronary disease, resting ejection fraction averaged .55 ± .03 (± SEM) During exercise left ventricular ejection fraction d not increase (.57 ± .03 NS versus resting) ith exercise 13 (42 per cent) had an increase of eft ventricular ejection fraction by at least .05 seven (22 per cent) had a decrease of ejection fraction by at least .05 and in 11 (36 per cent) ejection fraction was within ± .05 of control.

Seventeen men with coronary disease devel oped horizontal or down-sloping ST segment depression of at least 1 mm with exercise Left ventricular ejection fraction either decreased or failed to increase by .05 in all of these men (.56 ± 0.04 to .49 ± .03 $P < 0.05$) (Fig. 2) Of these 17 men, five had abnormal resting ejection fraction and 12 had normal resting ejection frac tion Twelve of these men had angina during exercise and five did not have angina. None of these men were able to achieve 85 per cent of their maximum heart rate prior to the development of ST depression.

Fourteen men with coronary disease did not have ST depression during exercise In these 14 men, left ventricular ejection fraction failed to increase with exercise in four men and increased normally (that is, ≥ .05) in 10 men (.53 ± .04 to .66 ± .04 $P < 0.01$) (Fig. 3) Four men had abnormal resting ejection fraction and in these le ejection fraction increased during exercise. The four men exercised for a shorter period of ti and to a lower heart rate than the normal me but for a comparable workload and heart rate other men with coronary artery disease.

Of nine men with coronary disease and abno mal resting left ventricular ejection fractio (< .47) four increased their ejection fractio during exercise and the other five had an abno mal response, that is, either no change or decrease of ejection fraction. The four with a increase of ejection fraction did not have ST segment depression. Of 22 men with normal rest ing left ventricular ejection fraction, seven had a increase of ejection fraction, and 15 had either decrease or no change in ejection fraction duri exercise. Of the seven with an increase of ejectio fraction, none had ST segment changes, where 12 of 15 with either a decrease or no change i ejection fraction had ST segment depressio Thus, three patients with normal resting ejectio fraction did not have ST segment depression, but did have an abnormal response of ejection frac tion to exercise.

Of the 15 normal men, two had ST segment depression with exercise All normals had an increase of ejection fraction during exercise including the two with electrocardiographic changes. These men should, perhaps, not be considered as entirely normal as they underwent cardiac catheterization for evaluation of chest pain and, as noted, two had "ischemic" ST segment changes with exercise. All of these men did have perfectly normal coronary arteriograms, normal resting and exercise ejection fraction, and normal resting segmental left ventricular contraction (contrast cineventriculography).

Discussion

In normal individuals, supine, dynamic exercise is associated with an increase in sympathetic activity and this results in an increase in heart rate, stroke volume, and left ventricular contractility [14] In normals ejection fraction increases as there is a small decrease in left ventricular end-diastolic volume and a large decrease in end-systolic volume.

In our patients with coronary disease an abnormal response of ejection fraction during exercise was frequently observed, and the ejection fraction during exercise was related to electrocardiographic ST segment depression. All men with ST

segment depression had either no increase or an actual decrease of ejection fraction during exercise. In the men with coronary disease who did not have ST segment depression with exercise, 28 per cent had an abnormal exercise ejection fraction. These results suggest that measurement of left ventricular ejection fraction increases the sensitivity of exercise testing in men with coronary disease.

Two of our 15 normal men developed ST segment depression during exercise. Both of these men had been shown to have normal coronary arteriograms and both had an increase of ejection fraction during exercise. The measurement of ejection fraction during exercise may increase the specificity of exercise testing by excluding men with falsely positive ST segment changes.

Sharma and associates[9] performed resting and post-exercise contrast left ventriculography in 17 men with coronary disease. Ten of 12 patients who had ST segment changes (≥ 1 mm. ST depression) with exercise either failed to increase ejection fraction or had a decrease in ejection fraction. In addition, an abnormal exercise response was observed in four of five patients with coronary disease who did not develop ST changes with exercise. Left ventricular ejection fraction increased in all four normal individuals studied.

Borer and associates[16] used an electrocardiographically gated radionuclide technique to record left ventricular ejection fraction at rest and during exercise. Ejection fraction increased in all normal subjects, but either decreased or was unaltered in all 11 patients with coronary disease. As in our study Borer and associates observed an abnormal exercise ejection fraction even with only a modest increase in heart rate.

In their patients with ST segment changes, Sharma and associates[9] observed ventriculographic abnormalities of regional left ventricular contraction in all 12 patients. These areas of abnormal contraction were associated with obstructive arterial lesions in the coronary artery supplying the region. Although an abnormal ejection fraction response to exercise was observed in four of five patients with coronary disease but without ST segment alteration with exercise, none of these patients had an exercise-induced regional contraction abnormality. Borer and associates[16] observed abnormal regional contraction abnormalities during exercise in all of their patients with coronary disease. All of these patients had normal resting ejection fraction and normal resting regional contraction. Thus, an abnormal ejection fraction response during exercise in patients with coronary disease appears to be associated with development of a regional left ventricular contraction abnormality.

These results suggest that measurement of left ventricular ejection fraction during exercise should increase the sensitivity and specificity of exercise testing to detect coronary artery disease. Left ventricular ejection fraction can be easily and safely measured using radionuclide techniques, either electrocardiographically gated or first transit methods. Both first transit[14, 15] and gated radionuclide methods[16] enable the observer to appreciate regional left ventricular performance, but whether or not this additional measurement increases the sensitivity or specificity beyond that of measurement of ejection fraction alone is uncertain at the present time.

Summary

Left ventricular ejection fraction (LVEF) was measured at rest and during supine bicycle exercise in 31 men with arteriographically defined coronary disease and in 15 normal men. LVEF was calculated from a left ventricular time vs activity curve (collimated scintillation probe, ^{99m}Technetium) as the fractional fall in count rate divided by the background-corrected left ventricular end-diastolic count-rate. In normal men LVEF at rest averaged .59 ± .06 (± SD) and during exercise was .72 ± .08. LVEF did not increase with exercise in men with coronary disease (.56 ± .03 to .57 ± .03, N = 31, AVE ± SEM, NS). In 17 men with coronary disease who had ST segment depression with exercise, LVEF either decreased or was unaltered in all (.55 ± .04 to .49 ± .03, $P < 0.05$) whereas in 14 without ST depression, LVEF increased in 10 (71 per cent) and was unaltered in 4 (29 per cent) (.54 ± .04 to .66 ± .04, $P < 0.01$). Results suggest that LVEF during exercise normally increases, but in men with coronary disease LVEF either fails to increase or actually decreases. In addition there appears to be a relationship between ST segment changes during exercise and ejection fraction.

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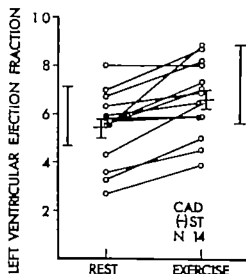


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Determination of pre and postoperative flow obstruction in patients undergoing closed mitral commissurotomy from non invasive ultrasound Doppler data and cardiac output

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The advent of surgical treatment of mitral stenosis has generated a demand for techniques able to quantify the flow obstruction in stenotic mitral valves and prosthetic mitral implants. The Gorlin formula allows the calculation of a valve area from the mean diastolic pressure gradient, diastolic duration per minute, and cardiac output this area is frequently used as a measure of the obstruction. Recent reports[2] have described an alternative technique whereby flow obstruction is quantified from non-invasive ultrasound Doppler data and cardiac output. The technique has the attractive feature that invasive procedures are necessary only to the extent that they are needed for cardiac output determination.

At this hospital valve replacement is generally the procedure used to relieve the flow obstruction in mitral stenosis. In selected patients, however closed mitral commissurotomy is performed. Indications for the latter procedure include insignificant regurgitation and absence of radiologic evidence of calcific valve deposits. In a recent study performed at this hospital, the ultrasound technique was used to determine the flow obstruction in a variety of mitral implants in the immediate postoperative period. The purpose of the present investigation was to use the technique to determine the pre- and postoperative flow obstruction in patients undergoing closed mitral commissurotomy and to compare the postoperative obstruction with that found in patients who had received mitral valve implants.

Methods

Theoretical considerations. In the steady flow through an orifice, Torricelli's law (equation 1)[4] closely predicts the pressure gradient if the Reynolds number is sufficiently large.

$$\Delta P = 1/2\, \epsilon V_{MAX} \quad (1)$$

where ΔP = pressure gradient, ϵ = mass density of fluid, and V_{MAX} = maximum fluid velocity It is a corollary of the law that V_M is constant over the cross-section of flow The ultrasound technique (as well as Gorlin s formula) assumes the validity of Torricelli s law for the flow in mitral stenosis.

Assuming the cross-section of flow at V_{MAX} as constant throughout diastole yields the following relationship,

$$\Delta P = 1/2\, \frac{\epsilon}{A_e} q \quad (2)$$

where ΔP = pressure gradient, ϵ = mass density of fluid, A_e = effective valve area, i.e., cross-section of flow at V_{MAX}, and q = diastolic mitral flow rate. Inspection of equation 2 demonstrates that A_e is a measure of the flow obstruction since this parameter defines the relationship between ΔP and q

Since V_{MAX} is assumed to be constant over A_e, simple mass continuity considerations yield

$$A_e = \frac{Q}{V_{MAX}\, T} \quad (3)$$

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Table I Patient data and numerical results

Pt no	Age (yr)	Sex		O.P	R	HR	PA	PCV	$\dot{Q}$	A	$\bar{A}$
			Preop.	1	SR	60	19	15	2.28	0.74	0.74
1	48	F	Postop.	2	SR	66	26	18	6.20	1.43	1 43
				3	SR	78	19	14	4.16	1.42	
			Preop.	1	AF	106	26	20	3 63	1.31	1.31
2	62	F		2	AF	95	19	14	4.19	1.66	
			Postop.	3	AF	90	16	12	3.72	1.36	1.45
				4	AF	100	16	6	4.11	1.22	
			Preop.	1	AF	130	38	33	3.63	0.96	0.96
3	60	F	Postop.	2	AF	106	28	19	4.38	1.57	1.67
				3	AF	130	11	4	3.90	1.77	
			Preop.	1	SR	61	16	11	4.68	1.26	1.26
4	62	M	Postop.	2	SR	90	21	16	6.84	2.26	2.16
				3	SR	99	23	15	8.03	2.07	
			Preop.	1	SR	125	22	17	4.95	1.36	1.36
5	32	M		2	SR	82	17	13	6.78	1.87	
			Postop.	3	SR	97	—	—	7 48	2.07	1.93
				4	SR	93	—	—	6.62	1.86	
			Preop.	1	SR	85	45	—	3.30	0.65	0.65
6	24	F	Postop.	2	SR	102	20	10	5.00	1.32	1.30
				3	SR	106	30	—	3.80	1.29	
			Preop.	1	AF	82	26	—	3.49	1.66	1.66
7	40	M	Postop	2	AF	93	—	—	4.41	2.33	2.46
				3	AF	88	—	—	5.83	2.59	
			Preop.	1	SR	8	36	28	4.81	0.79	0.79
8	29	F	Postop.	2	SR	82	36	21	7.53	1.38	1.30
				3	SR	104	—	—	4.53	1.19	

[illegible]breviations O.P = observation period, R = rhythm, HR = heart rate, PA [illegible] mean pulmonary artery pressure (mm. Hg), PCV = mean pulmonary capillary venous pressure (mm Hg), $\dot{Q}$ = cardiac output (L/min), A = effective valve area (cm.) $\bar{A}$ = mean effective valve area (cm) SR [illegible] sinus rhythm, AF = atrial fibrillation

where A = effective valve area (cm) Q = mitral flow/minute (cm. /minute) $\bar{V}_{MAX}$ = mean diastolic maximum blood velocity (cm./sec.) and T = diastolic duration/minute (sec)

2 MHz, non invasive ultrasound Doppler systems can register the frequency shifts from the diastolic mitral jet in mitral stenosis. Performing a frequency analysis of the obtained frequency shifts identifies the diastolic time course of the maximum frequency shift (Δf) The relationship between Δf_{MAX} and V_{MAX} is expressed by the Doppler equation

$$V = \frac{c \ \Delta f}{2 \ f \ \cos \Theta} \quad (4)$$

where V = maximum blood velocity c = velocity of sound in blood Δf_{MAX} = maximum frequency shift, f = frequency of incident sound beam, and Θ = angle between axis of incident sound beam and velocity vectors of V_{MAX} If the ultrasound probe is positioned such that cos Θ = 1 in the Doppler equation, the time course of V_{MAX} can be determined from Δf_{MAX}.

For a 2 MHz instrument the frequency shifts from the jet in mitral stenosis are well within the audible range and inspection of equation 4 demonstrates that the audio signal of the frequency shifts contains the largest amount of high frequency sound when cos Θ = 1. Thus, in any given patient the optimum probe position can be identified by performing an audio-manual scanning procedure that identifies the probe position where the audio signal seems to contain the largest amount of high frequency sound.

Patient material The patient material consisted of eight adults with pure mitral stenosis who had been selected for closed mitral commissurotomy (digital splitting of the commissures). Table I presents further patient data.

Ultrasound equipment. A modified 2.1 MHz Hewlett Packard Sound Monitor was used to obtain the frequency shifts from the mitral blood stream. The data were recorded on magnetic tape and were subsequently frequency analyzed on a Kay Sona-Graph Sound Spectrograph.

Thermodilution system A multichannelled indwelling catheter was used to determine cardiac output. The catheter was inserted preoperatively via a cubital vein and the catheter tip was positioned such that it floated freely in a pulmonary artery Cardiac output was determined with the thermodilution principle by rapidly injecting 10 cm. of 5 per cent glucose solution at 0° C into the superior vena cava via one of the catheter channels. Cardiac output was computed electronically and presented as a digital display The catheter was part of a system (Swan Ganz) capable of determining pulmonary artery pressure, pulmonary capillary venous pressure and cardiac output.

Collection of data Data were collected intermittently during 5 to 10 minute periods (observation periods) During an observation period ultrasound data from 10 to 20 consecutive beats and cardiac output were recorded 3 to 4 times. Prior to the collection of ultrasound data, the region of the mitral valve was scanned with the ultrasound beam and the probe position where the audio signal of the diastolic frequency shifts seemed to

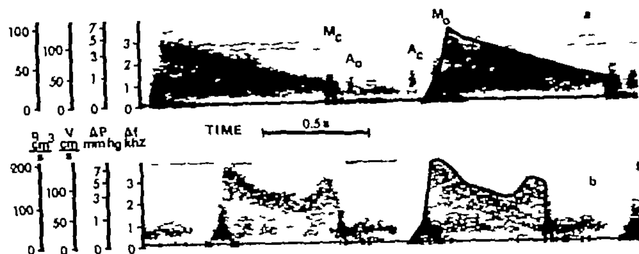


Fig. 1 *Frequency shifts (Δf), diastolic pressure gradients (ΔP), diastolic blood velocities (V), and diastolic flow rates (q)* from patient No. 1 (sinus rhythm). The curves on sloping blackened diastolic areas represents maximum diastolic frequency shift, diastolic pressure gradient, maximum diastolic blood velocity and diastolic flow rate; in the last diastolic period this curve has been hand-drawn. The presentation is nondirectional. *Blackened vertical columns are due to valve motion, M_o, M_c, A_o, and A_c = mitral and aortic valve opening and closing motions,* respectively. Blackened systolic areas represent velocities in left ventricular outflow tract. *a*, Observation period 1 (preoperative). Effective valve area = 0.74 cm. Atrial contraction presumably occurs after closure of mitral valve. *b*, Observation period 2 (postoperative). *Effective valve area* = 1.43 cm. Note effects of atrial contraction.

contain the largest amount of high frequency sound identified. With the probe in this position ultrasound data were recorded. In each patient there was one preoperative observation period and 2 to 3 postoperative observation periods. The preoperative observation period took place in the operating theatre during induction of anesthesia and the postoperative observation periods took place in the intensive care unit during the first 2 to 3 postoperative days. Observation periods were generally 12 to 24 hours apart. Mean pulmonary artery pressure and mean pulmonary capillary venous pressure were generally determined at the termination of each observation period. The multiple postoperative observation periods and the multiple data collections within each observation period were performed in order to enhance the accuracy of the obtained results.

Determination of effective valve area Three to four consecutive beats from the early, middle, and late part of each observation period were frequency analyzed on the Spectrograph. The frequency analyses (Figs. 1 to 3) allowed the identification of the diastolic time course of Δf_{MAX} and also the determination of the parameter T (equation 3). The mean diastolic value of Δf_{MAX} and the mean value of T was determined for each observation period. The mean diastolic value of V_{MAX} was then determined from the Doppler equation (equation 4) using c = 1570 10^3 cm./sec., f = 2.1 MHz, and cos Θ = 1. The value of A_e for each observation period was then determined from equation 3 using the mean value of cardiac output as Q.

For illustrative purposes the time course of ΔP was determined from Δf_{MAX} in some patients (Figs. 1 to 3) using ϵ = 1.06/981 g-sec. /cm. in equation 1. For the same purpose the time course of the instantaneous diastolic mitral flow rate was determined in one patient (Fig. 1) by assuming constant A_e throughout diastole.

Results

Frequency analyses of the recorded frequency shifts allowed identification of pre- and postoperative time course of diastolic Δf_{MAX} in all patients. Generally, the frequency analyses also displayed systolic frequency shifts due to blood velocities in the left ventricular outflow tract and frequency shifts due to mitral and aortic valve motion. Representative frequency analyses are presented in Figs. 1 to 3. The assumptions underlying the ultrasound technique allow the placement of four different ordinates on the frequency analyses: in Fig. 1 this is shown for illustrative purposes. In Figs. 2 and 3 only the diastolic pressure gradient has been used as ordinate.

The effective valve area increased postoperatively in all patients, preoperative value

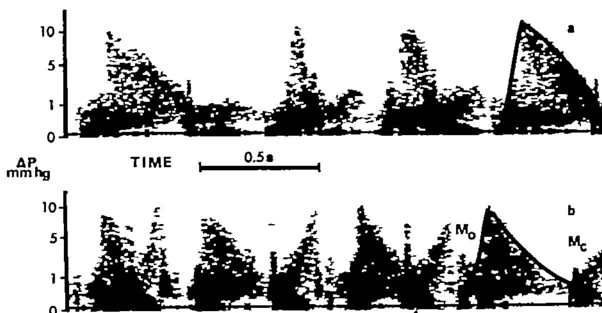


Fig. 2. Diastolic pressure gradients (ΔP) from patient No. 2 (atrial fibrillation). M and M — representations of mitral opening and closing motion. The curve enveloping blackened diast lic areas represents pressure gradient in the last diastolic period this curve has been hand-drawn. a, Observation period 1 (preoperative). Effective ah e area = 1.31 cm. b Observation period 3 (postoperative). Effective ah e area = 1.36 cm. Blackened systolic areas may represent velocities in regurgitating flow

was 1.08 ± 0.34(SD) cm. increasing to 1.71 ± 0.43(SD) cm. postoperatively (Table I) Cardiac output also increased postoperatively all patients preoperative value was 8? ± 0.89(SD) L./minute and postoperative value was 5.55 ± 1.39(SD) L./minute. Mean pulmonary artery pressure and mean pulmonary capillary venous pressure did not demonstrate a similar uniform postoperative response. In any given patient there were relatively small variations in the values of A, obtained in the multiple postoperative observation periods (± 6(SD) per cent).

The postoperative systolic frequency shifts in patient No. 2 were relatively large and might be due to mitral insufficiency (Fig. 2) Patient No 2 also had the smallest postoperative increase in A, (0.14 cm.) and the largest variation in postoperative A, (0.34 cm.)

Discussion

The ultrasound technique and Gorlin s formula are both based on Torricelli s law This law represents a steady flow orifice equation and thus neglects the inertial component of the pressure gradient. When the entire diastolic period is considered, however inertial effects tend to cancel each other In addition, when flow obstruction is considered it is the dissipative (frictional) component of the gradient that is of chief interest, and previous studies have shown that the law predicts this component closely in mitral stenosis. Thus, Gorlin and Gorlin performed hydraulic tests on an excised stenotic mitral valve and found a quadratic relationship between pressure gradient and flow rate Holen and associates forced whole blood at room temperature through orifices of various sizes and found a quadratic relationship between pressure gradient and V_m at Reynolds numbers expected in mitral stenosis. Whamond and Taylor[a] studied the velocity profile in mitral stenosis at the level of the annulus and found it basically flat.

The ultrasound technique makes the additional assumption that the ultrasound probe is positioned such that cos Θ = 1 in the Doppler equation. Holen and Simonsen made simultaneous manometric and ultrasound registrations in patients with mitral stenosis and compared results from identical diastolic periods. The mean diastolic manometric gradient (determined from left atrial and left ventricular pressures) was found to agree closely with the corresponding gradient calculated from ultrasound data using

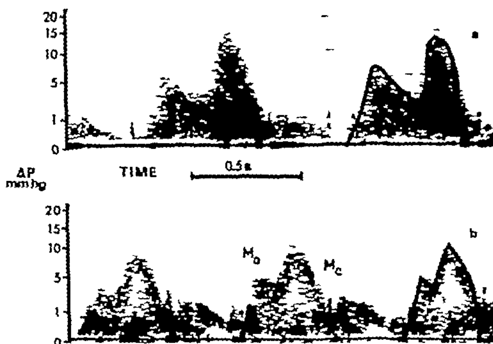


Fig. 3. Diastolic pressure gradients (ΔP) from patient No. 4 (sinus rhythm). M_o and M_c = representations of mitral opening and closing motion. *a*, Observation period 1 (preoperative). Effective valve area = 1.26 cm. *b*, Observation period 2 (postoperative). Effective valve area = 2.26 cm. Note prominent effects of atrial contraction both pre- and postoperatively

Torricelli's law. The results of the latter study thus demonstrated that the employed audio-manual scanning technique effects an optimum probe placement and also provided further evidence of the validity of Torricelli's law in mitral stenosis. A similar study of patients with an assortment of mitral valve implants has also shown a close agreement between the two mean diastolic gradients (unpublished). The relationship between probe position and the obtained value of V_{max} has not been systematically studied, but experience with the ultrasound technique has indicated that the obtained value of V_{max} is not nearly as dependent upon probe position as might be expected from inspection of the Doppler equation. This observation indicates that the velocity vectors of V_{max} have a number of different directions within the left ventricle, a situation which makes it relatively easy to obtain a satisfactory probe placement.

The Gorlin formula is generally used in the form,

$$A_v = \frac{Q}{31 \cdot T \cdot \sqrt{\bar{\Delta}P}} \qquad (6)$$

where A_v = valve area, Q = mitral flow rate, T = diastolic duration/minute, and $\bar{\Delta}P$ = mean diastolic pressure gradient. The constant 31 has incorporated a factor that relates A_e and A_v. It has previously been estimated that $A_e/A_v \approx 0.6$. Hammermeister and colleagues suggested on the basis of experimental evidence that the constant be changed to 40, the factor then becomes $A_e/A_v \approx 0.78$. The ratio of A_e and the actual valve area can be expected to vary from patient to patient, and the ratio is certainly not identical in mitral stenosis and mitral valve implants. It is therefore reasonable to simply use A_e as a measure of the flow obstruction as has been done in the present investigation.

In applications of equations 3 and 6 mitral flow rate is generally assumed identical to cardiac output. When mitral insufficiency is present, this latter assumption is clearly invalid and the obtained values of A_e or A_v will be smaller than that representing the actual flow obstruction. It is thus possible to reduce the obstruction in mitral stenosis by performing a commissurotomy and yet obtain the same pre- and postoperative values of the obstruction because of a surgically generated insufficiency. This phenomenon may

explain the small increase in A_e found in patient No. 2. The large range in the postoperative values of A_e observed in this patient may be due to a changing regurgitant fraction

In a recent study[5] the ultrasound technique was used to quantify the flow obstruction in an assortment of mitral valve implants in the immediate postoperative period. The following values of A_e were found (valve size in parenthesis)

Björk-Shiley = 2.07 cm. (31) 2.24 cm (29) 1.65 cm (27)

Hancock = 1.96 cm (31) 1.39 cm (29) 1.24 cm. (27)

Lillehei Kaster = 2.33 cm. (25) 1.41 cm. (20)

A comparison of the results of the present investigation with the values presented above demonstrates that in the immediate postoperative period the flow obstruction in patients who have undergone closed mitral commissurotomy is of the same order of magnitude as the obstruction in patients who have received mitral valve implants.

Conclusions

Theoretical considerations and results of previous studies indicate that in the quantification of mitral flow obstructions non invasive ultrasound Doppler data can be substituted for manometric data without loss of accuracy Non invasive procedures have many obvious advantages in the present investigation the combination of ultrasound data and data from the indwelling catheter system allowed repetitive collections of relevant data under circumstances where the application of manometric methods would be both difficult and hazardous. The numerical results of the investigation are reasonable and indicate that in the immediate postoperative period the flow obstruction in patients who have undergone closed mitral commissurotomy is of the same order of magnitude as the obstruction in patients who have received mitral valve implants.

Summary

A non invasive ultrasound Doppler system and an indwelling thermodilution catheter system were used to determine the pre- and postoperative mitral flow obstruction in eight adults undergoing closed mitral commissurotomy The effective valve area (A_e) was used as a measure of the obstruction. In the eight patients A_e was 1.08 ± 0.34(SD) cm. preoperatively and increased to 1.71 ± 0.43(SD) cm. postoperatively The technique used in the investigation appears useful for the evaluation of surgical procedures designed to reduce the mitral flow obstruction.

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Case reports

Sleep apnea and Q-T interval prolongation—a particularly lethal combination

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Sudden unexpected death in infancy is the leading cause of death in infants between one week and one year of age. The investigation of sudden unexpected death in infancy often yields no obvious cause of death and results in the autopsy diagnosis of sudden infant death syndrome (crib death, cot death, SIDS). *This syndrome, however* has been properly defined and correlated with several factors. Recent research has centered around cardiac arrhythmias and apnea as the predominant final common pathways for sudden unexplained death in infancy. Other authors[1] have proposed a link between apnea and cardiac arrhythmias, both being necessary components of the sudden death. We have discovered a 20-day-old *infant who died with* an autopsy diagnosis of SIDS that demonstrated evidence of chronic hypoxemia consistent with recurrent bouts of apnea. The child also died during an hypoxic episode and had demonstrated a prolonged Q-T interval in an electrocardiogram taken at one day of age (Fig. 1). We believe this case to be unique in providing a link between cardiac and respiratory mechanisms of death in a SIDS victim.

Case report

A term birth female infant weighing 3.6 kilograms was born in City of Memphis Hospitals to a 21-year-old Gravida III Para III black female. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. At one day of age, respirations were 60 per minute and slightly irregular. An electrocardiogram (ECG) (Fig. 1) at this time was interpreted as showing a sinus arrhythmia, left axis deviation, and left ventricular hypertrophy. No mention of the Q-T interval was made.

The child was discharged at two days of age without diagnosis and the mother was instructed to return with the child in three weeks for reexamination. At 20 days of age, the child was discovered lifeless in its bed and was brought to the morgue. On arrival, a rectal temperature of 28.5°C., an aortic blood PO_2 of 4 mm. Hg and a serum calcium of 13.6 mg. per 100 ml. were obtained. Gross examination of the viscera revealed slightly increased total heart weight of 24.3 grams in relation to a body weight of 4.15 kilograms, a left ventricle of normal thickness, but a *slightly hypertrophied right ventricle being* 3.5 to 4 mm. thick. Heart valve measurements were within normal limits. The lungs were both congested, the right lung weighing 48.5 grams and the left lung weighing 39.3 grams, *with both lungs demonstrating a moderate amount of pulmonary* edema on histologic examination. The medial area of pulmonary arterioles (30 to 100 μm diameter) was shown to be significantly increased using a point-count method described elsewhere. No histologic abnormalities were noted in any of the other organs including selected sections of the cardiac conducting system.

Reexamination of the ECG mentioned previously (Fig. 1) showed a heart rate of 160 per minute and an uncorrected Q-T interval of approximately 0.30 sec. using Lead V. Using Bazett's formula, the Q-T interval corrected for heart rate of Q-Tc equals 0.48 sec.

Discussion

There are two important but yet distinct processes under consideration here, namely the phenomenon of apnea-induced hypoxia and prolongation of the Q-T interval. Both of these events have been implicated in contributing to SIDS.

Naeye[2] has studied the effects of hypoxia in infants, and has correlated the findings in SIDS

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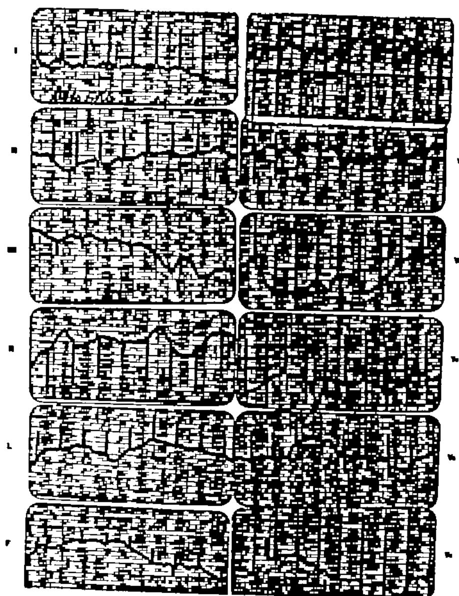


Fig 1 The electrocardiogram of one-day-old infant with prolonged Q-T interval.

victims to identical changes seen in those infants suffering from chronic hypoxemia Naeye[9] relates that hypoxia can result in pulmonary hypertension and eventually cor pulmonale. Two anatomic correlates of this condition are right ventricular hypertrophy and thickened media in pulmonary arterioles, and both were demonstrated in this patient. Shaw presented one possible explanation for this hypoxia by demonstrating that many infant humans are obligate nose breathers. Nasal obstruction in infants as occurs in an upper respiratory tract infection might readily produce an obstructive apnea result ing in a hypoxic state. Thi h pothesis is still attractive in spite of the lack of evidence of nasal obstruction in SIDS victims Mason and coworkers[13] have demonstrated that about one half of SIDS victims die in respiratory failure and another half die in circulatory failure. As illustrated by Mithoefer and colleagues,[14] postmortem oxygen tensions reflect premortem values if determined within six hours of death. Even though our infant had been dead for approximately eight hours, we believe the postmortem PO_2 of 4 mm. Hg to represent antemortem hypoxic hypoxemia, because this is well below the 6 hour discriminating value of 16 mm. Hg. Given a normal rate of decrease, the 6 hour value would not have exceeded 8 mm. Hg. The degree of hypoxemia in this case makes the speculation that this infant suffered an apneic episode an attractive one

Tilkian and associates have shown how

obstructive apnea can produce cardiac arrhythmias which are reversible when tracheostomy obviates the obstruction. The arrhythmias reported by Tilkian and co-workers[14] are noted to be mainly of sinus rate change and therefore relatively benign. Guntheroth[16] points out that marked bradyarrhythmias seen in patients reported by the Stanford group are essential and normal components of the dive reflex. This reflex, when overactive, has been implicated as contributing to SIDS. However Tilkian and associates[14] have also demonstrated periodic asystole, second degree A V block, complex premature ventricular contractions, and ventricular tachycardias in patients with obstructive apnea, none of which can be termed benign arrhythmias.

It was noted that our infant possessed a prolonged Q-T interval in an electrocardiogram at one day of age (Fig. 1) Alimurung and collaborators[18] listed the corrected Q-T interval (Q-T) value for children up to 1 month of age as 0.386 sec. with a standard deviation of 0.019 sec. Thus our infant with a Q-T of 0.48 sec. had a significantly prolonged Q-T interval. Alimurung and associates[18] also noted that hypocalcemia, hypokalemia, rheumatic carditis, spasmophilia, hypertension, heart failure, diptheria, quinidine intoxication, nephritis, and cretenism are causes of Q T interval prolongation. Lepeschkin and Surawicz,[17] however point out that hypokalemia falsely prolongs the Q-T interval with an enhanced U wave merging with and apparently prolonging the T wave. The previously mentioned calcium level of 13.6 mg. per 100 ml. rules out hypocalcemia as a cause of Q-T interval prolongation in this case.

There have been numerous studies delinlating the contribution of congenital Q-T interval prolongation to sudden death with the Jervell Lange-Nielson[20] and Romano-Ward[21, 22] syndromes serving as the classic examples of the long Q-T syndrome as defined by Schwartz and colleagues.[23] Schwartz and Malliani[24] implicate the long Q-T syndrome as a cause of SIDS and point out that T wave alternation is a phenomenon seen with Q-T interval prolongation. Significantly in the case presented here, T wave alternation is noted in Leads I, II, and V (Fig. 1)

To determine whether this infant had the inherited form of Q-T interval prolongation, a family study was instituted. Electrocardiograms of the mother a 4-year-old sibling, and a 2 year-old sibling revealed Q-T values of 0 40, 0 41, and 0.42 seconds, respectively These corrected Q T intervals while not prolonged, are at the upper limit of normal of 0.42 sec. and are consistent with the prolonged Q-T interval found in our infant.

Q-T interval prolongation is a disorder of myocardial repolarization allowing for the development of ectopic excitatory foci which increases the vulnerability to a fatal episode of ventricular fibrillation. In normal individuals, stresses such as catecholamine release during exertion and hypoxia tend to shorten the Q-T interval.[25] However in those individuals with the long Q-T syndrome, hypoxia, fright, and exertion cause an increase in an already prolonged Q-T interval.[11, 24] Schwartz and colleagues[23] postulated that this phenomenon is due to an imbalance in the right and left heart sympathetics as modulated by the respective stellate ganglia. Thus, as predicted by Schwartz,[24] a prolonged Q-T interval while potentially fatal alone, is made even more lethal during periods of stress. Hypoxia, as might occur during a period of sleep apnea with an infant struggling to breathe, would be such a stress.

Summary

We have discovered a 20-day-old infant who possessed anatomic evidence of chronic hypoxemia with right ventricular hypertrophy and who died in hypoxic hypoxemia with a postmortem PO_2 of 4 mm. Hg. Subsequently and ECG was discovered which had been obtained at one day of age and showed Q-T interval prolongation along with T wave alternation. We believe this case to be one of the first to substantiate the mechanism for SIDS as proposed by Schwartz,[24] with hypoxia acting synergistically with a prolonged Q-T interval causing sudden unexpected death in this infant—providing a link between cardiac and respiratory mechanisms of death.

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Post traumatic coronary occlusion and early left ventricular aneurysm

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Several cases of transmural myocardial infarction and ventricular aneurysm caused by a blunt trauma of the chest have been reported. Nevertheless, the cases with coronary and ventricular angiography are very few. There has always been a great debate on the etiological mechanism of such lesions. As in some cases there was no evidence of coronary lesions, it was postulated that they were produced by direct myocardial contusion, but in other instances the evidence of coronary occlusion was angiographically and pathologically proved.

We report one more case of blunt trauma of the chest in which a coronary angiography revealed a complete cut-off of the left anterior descendent coronary artery and a left ventriculogram showed a huge ventricular aneurysm.

Case report

The patient, 38-year-old white male with no pertinent past history sustained blunt trauma of the chest on July 25, 1977. He was driving his car when piece of one of the rear wheel suspensions (C spring) from an old truck ahead of him broke and was released, sped towards his windshield, smashed it, and hit his anterior chest causing blunt trauma. He was unconscious for few minutes and there was severe oppression retrosternal pain lasting 24 hours. He was admitted to Community Hospital where he presented progressive dyspnea, orthopnea, and bloody sputum. As the clinical situation worsened, five days later on July 30th, he was transferred to our hospital where he was immediately admitted to the coronary care unit. On admission he was conscious, pale, in a cold sweat, and very dyspneic. In the upper third of the sternal region the skin showed small area of slight echymosis. His blood pressure was 100/70 mm. Hg, pulse regular at 130/minute, and temperature 37.5° C. On auscultation there were wheezes in both pulmonary fields and also râles, mainly in the right base. Examination of the heart revealed a prominent area of dyskinesia at the apex; there was a left ventricular gallop and no murmurs, clicks, or pericardial rubs were elicited. The chest film showed a severe cardiomegaly and vascular and alveolar pattern of pulmonary edema, mainly in the right side. The ECG revealed regular sinus rhythm of 130/minute, AP = 60 degrees, AQRS = −60 degrees, P of 0.06 sec., QRS of 0.10 sec., and PR interval of 0.14 sec. There was evidence of an acute anteroseptal myocardial infarction with lateral extension and anterior hemiblock. A VCG confirmed the electrocardiographic findings. Laboratory data gave a CPK of 67 mU./ml., SGOT of 44 mU./ml., GPT of 60 mU./ml., and LDH of 678 mU./ml. with increased 1-2 fractions of the isoenzymes. Total lipids were 633 mg. per cent, cholesterol was 188 mg. per cent, triglycerides were 82 mg. per cent, and there was normal lipid electrophoresis. A lung gammagraphy was normal. The echocardiogram ruled out any pericardial effusion and showed prominent hypokinesis of the posterior wall of the left ventricle at the level of the recording of cordae tendineae of the mitral valve, decreasing progressively towards the apex where the myocardium of the posterior left ventricular wall was akinetic. The septum was also akinetic. The end-diastolic diameter of the left ventricle was 6.1 cm.

The patient, despite digitalis and diuretic therapy made poor progress. There was no real improvement in the clinical, radiological, and hemodynamic findings of his ventricular failure. On August 9 he fell into ventricular fibrillation and cardiac arrest, with full recovery after 400 watt/sec. discharge.

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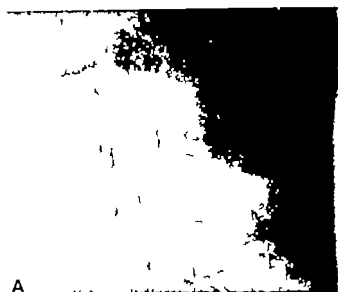




Fig. 1. A, Left coronary arteriography in the right anterior oblique projection. A complete cut-off of the left anterior descending coronary artery at its origin can be seen. No other lesion is observed. B, Right coronary angiography in the left anterior oblique projection. The view appears normal.





Fig. 2. A, Left end-diastolic ventriculogram in the right anterior oblique projection. A huge anteroapical aneurysm of the free ventricular wall is seen. The apical filling defect could indicate a possible mural thrombus. B, Left end-systolic ventriculogram in the right anterior oblique projection. Only the posterobasal segment contracts normally.

On August 18 cardiac catheterization was performed, giving the following findings.

1. Complete cut-off of the left anterior descending coronary artery at 1 cm. of its origin. Otherwise no abnormalities were found in the coronary tree (Figs. 1A and B).

2. A huge aneurysm of the free wall of the left ventricle with possible mural thrombus (Figs. 2A and B).

3. Left ventricular function was severely impaired: the end-diastolic volume was 387 ml./M.², end-systolic volume was 332 ml./M.², systolic volume was 45 ml./M.², ejection fraction was 11 per cent, ejection fraction of the contractile region (Watson method) was 38 per cent and end-diastolic pressure was 33 mm. Hg.

As he was in a state of refractory left ventricular failure and he had already had an episode of ventricular fibrillation, he was scheduled for surgery. Before the operation could be performed (resection of the aneurysm), he signed out and went home, where six months later he was still alive although bedridden, in Class IV failure despite medical treatment.

Discussion

It was thought that the coronary arteries were resistant to blunt thoracic traumas and, hence, that coronary thrombosis was an unlikely cause of traumatic ventricular aneurysms. There is a question as to what triggers the series of

events following a blunt trauma to the chest causing a myocardial infarction. Some reports demonstrate—pathologically and angiographically—the laceration [11] or thrombosis[1,2,3,10] of the coronary arteries with release of an atheromatous plaque ending in occlusion of the vessel, on the other hand, the infarction might also be due to a tear in the intimal layer of the artery without there being any previous atheromatous damage. Other reports postulate the possibility of a myocardial contusion as the real cause of the myocardial necrosis and ventricular aneurysm, since the authors found a normal coronary angiography

Myocardial contusions can mimic electrocardiographic changes of ischemia or transmural infarcts. [14] The electrocardiographic pattern of transmural infarct recorded in our patient could be explained by a myocardial contusion without any coronary lesion, nevertheless, the coronary angiography performed in the third week after the trauma revealed a complete cut-off of the left anterior descending coronary artery at its proximal segment. It was the only lesion observed. Although it is not possible to rule out a preexisting lesion of the left anterior descending artery we think that the blunt trauma of the chest bears a cause-effect relationship to the complete occlusion of this artery

Only a few cases of resection of traumatic aneurysms have been reported, [12] [16] and it is difficult to decide the appropriate time for surgical intervention. In 1970, Pupello and colleagues[15] encountered surgical problems because friable tissue and sutures were loose in a traumatic aneurysm operated on in the sixth week. In 1977 Berkoff and associates[16] had no problems in the surgical procedure of a 15-week-old traumatic aneurysm, on finding a solid fibrous tissue. This surgery is not comparable to the resection of a postinfarction aneurysm[18-20] the timing in the latter case is different because these aneurysms are usually operated on in the chronic phase. According to Mallory and co-workers,[17] it is advisable to wait from 3 to 6 months for aneurysmectomy because with that delay the aneurysm will probably be completely fibrosed, well localized, and hence more suitable for surgery

To summarize, this is a case of coronary occlusion and early left ventricular aneurysm secondary to a blunt chest trauma. Because of the severity of left ventricular failure which was refractory to medical management, the rapid deterioration of the clinical situation, and episode of ventricular fibrillation plus a possible mural thrombus observed in the ventriculogram, we were prompted to advise surgery Despite the poor prognostic risk and despite the fact that the patient was only in the fourth week following trauma, we thought surgery was the only opportunity of survival he could be offered. The patient declined the operation and three months later he was alive, in functional Class IV This raises the question of whether the aneurysmectomy is advisable in an early phase of its evolution. In fact, until more cases of this kind are reported, the time for surgery will remain a matter of doubt and decisions will be made on an individual basis.

Summary

A case of post-traumatic coronary occlusion is presented. A 38-year-old male sustained a blunt chest trauma with secondary transmural infarct and early evolution toward a huge left ventricular aneurysm. Coronary arteriography showed complete occlusion to the left anterior descending coronary artery

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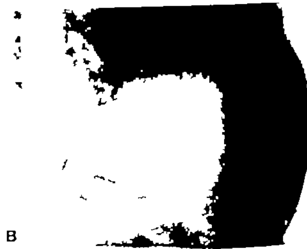


Fig. 2. *A*, Left end-diastolic entriculogram in the right anterior oblique projection. A huge anteroapical aneurysm of the free entricular wall is seen. The pical filling defect could indicate a possible mural thrombus. *B*, Left end-systolic entriculogram in the right anterior oblique projection. Only the posterobasal segment contracts normally.

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Clinical pathologic conference

Peter Harris, M.D., Ph.D., F.R.C.P.
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PROFESSOR HEATH An elderly Negro aged 73 years, was admitted to hospital as an emergency case at 10.30 P.M. on October 8, 1977 on account of breathlessness which had become progressively more severe over the preceding 24 hours. During that time he had had a persistent cough which was productive of a frothy blood-stained sputum. He said that since April, 1977 he had experienced attacks of palpitation in which his heart beat had been rapid and irregular. These attacks occurred once every few weeks and lasted about ten minutes; sometimes they were followed by unconsciousness. They were associated with pain in his chest and in the pit of the stomach. For two weeks he had noticed that he had become breathless while dressing. He needed to be propped up with four or five pillows at night so that he could sleep. For two weeks before admission his ankles had been swollen. For months he had suffered with nocturia. He had been born in Liberia and came to Britain in 1926. He had separated from his wife and lived alone. He did not smoke or drink alcohol.

On examination there was pitting edema of both ankles. The jugular venous pressure was raised. The systemic blood pressure was 130/80 mm. Hg. The radial pulse was irregular and the rate was just under 100 per minute. The apex beat was felt in the seventh left intercostal space just beyond the mid clavicular line. There was a faint apical systolic murmur. There were bilateral basal crepitations. The edge of the liver could be felt four finger breadths below the left costal margin. The spleen was not palpable. On examination of the central nervous system no abnormality could be found. In spite of treatment his breathlessness worsened and he died on October 10, 1977.

Investigations. Smears of sputum stained by the Ziehl-Neelsen technique did not contain tubercle bacilli.

PROFESSOR HARRIS The history of progressively more severe breathlessness over the day preceding admission to hospital, associated with a persistent cough productive of frothy blood stained sputum, implies a raised pulmonary venous pressure which had led to pulmonary edema. The history suggests that this condition had been developing for some weeks. The pulmonary circuit is particularly sensitive to edema. The principles which govern its formation are those of the Starling equation, namely hydrostatic against osmotic pressure. Hence any elevation of pulmonary venous pressure is likely to give rise to edema. The clinical findings of pitting edema of both ankles, a raised jugular venous pressure, and enlargement of the liver can only lead to the conclusion that congestive heart failure was present. I use this term instead of "right heart failure," which is a misnomer. The principles which underline the development of edema in the systemic circulation in this condition are not simply those of the Starling's equation. In congestive cardiac failure there is a retention of fluid and electrolytes in the body due to the response of the kidney to a persistently low cardiac output. The condition is similar to the renal shut-down which occurs in surgical shock. The attacks of rapid and irregular heart beat suffered by this patient were sometimes followed by unconsciousness. A normal heart can sustain a great increase in heart rate without the patient losing consciousness, but, in a diseased heart, a tachycardia will more readily reduce the cardiac output to the extent that the cerebral blood flow is insufficient and consciousness is lost. The possible cause of the arrhythmia I will return to in a moment.

We must look for some lesi left and

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Fig. 1. Posteroanterior radiograph of the chest taken on October 8, 1977.

the heart to account for the persistently low cardiac output and raised pulmonary venous pressure. The radial pulse is described as irregular and thus could have been simple ectopic beats or atrial fibrillation. The character of the carotid pulse would be of interest, for this is less influenced by the peripheral arterial system. In particular I should like to know how full it was and whether there was any anacrotic notch. A slow up-stroke might suggest a diagnosis of aortic stenosis.

The systemic pressure reported as 130/80 mm. Hg is normal, but of course he could have had systemic hypertension and some event in his illness had led to a fall in the pressure. Was there any evidence of sustained systemic hypertension in the retinae?

The apex beat was in the seventh left intercostal space just beyond the mid-clavicular line and the fact that the apex had been shifted downwards and a little outwards suggests that we are dealing with enlargement of the left ventricle.

A faint apical systolic murmur was reported. One would like to know whether this murmur occupied the whole of systole, as you would expect with mitral incompetence, or was it of the ejection type which one would anticipate with aortic stenosis? Both murmurs would be audible at the apex but that of aortic stenosis would also be heard in the aortic area and would be transmitted into the neck. The apical systolic murmur reported could also come from an incompetent tricuspid valve, in which case it would get louder on inspiration in contrast to the murmur of mitral incompetence which would get louder on expiration. In the case of tricuspid incompetence there would likely be an associated systolic expansion of the liver.

In considering lesions of the left side of the heart which could give rise to the clinical picture presented, we have first of all to consider those valvular conditions which interfere with filling of the left ventricle. This could be due to rheumatic heart disease of the mitral valve, but one would hardly expect florid rheumatic heart disease to present in a man of 73 years without a much longer history. The "floppy" or myxomatous mitral valve leads to mitral incompetence which may be progressive and present at this age. At least in the early stages of this disease, one would find a late systolic murmur and a systolic click, neither of which were reported in this patient. Bacterial endocarditis of the mitral valve has to be kept in mind, for it is becoming clear with the passage of time that this disease may affect the old as well as the young. In this case there were no other clinical indications of this condition. There could be some condition causing an increased afterload of the left ventricle, such as aortic valve disease. However, there is really no evidence of aortic valve stenosis or incompetence. Furthermore we have seen that systemic hypertension is unlikely to have been the cause of this man's condition.

All of these negative findings lead me to believe that we must consider the state of the left ventricle itself. By far the commonest cause of damage to this chamber of the heart is ischemic disease. In this case the disease of the myocardium may have become associated with mitral incompetence due to papillary muscle dysfunction, or to rupture of one of the chordae tendineae. There is, however, no convincing history of pain in the chest which you would anticipate occurring with ischemic heart disease. Admittedly he had been getting pains during the attacks of palpitation but this could be readily ascribed to swelling of the liver. I am of course aware that ischemic heart disease, even of this severe form with left ventricular failure, can be present in a patient in whom there has been no history of an acute myocardial infarction or angina, but the absence of a history of anginal pain forces one to be chary of making the diagnosis. Certainly the attacks of arrhythmia would fit in well with ischemia.

The other and much rarer form of disease of the

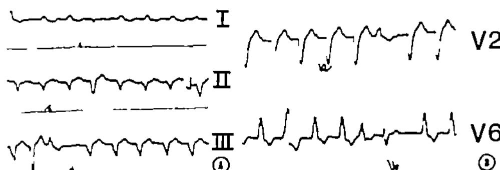


Fig. 2, A and B. Strip chart showing six leads from an electrocardiographic tracing taken on October 10, 1977

left ventricle which one has to consider is cardiomyopathy which would be of the "congestive" rather than the obstructive type. This is presumably not due to alcohol, for we are specifically told that he was an abstainer. He is a Negro from equatorial Africa and this is of interest, for cardiomyopathies are common in this area, particularly endomyocardial fibrosis. On the other hand he has been in Britain since his early twenties. Cardiomyopathy is sometimes familial, but we have no evidence from the clinical summary that other members of his family were affected.

The logical conclusion is that this patient had widespread damage to the myocardium. In real life, there is no doubt that the probabilities would be in favor of chronic ischemic heart disease. In the world of the CPC however probabilities have a different distribution and my diagnosis would be that of cardiomyopathy.

DR. WILSON. In answer to Professor Harris's queries concerning the physical signs there was nothing in the arterial pulse to suggest aortic valve disease and the retinae gave no evidence of pre-existing systemic hypertension.

PROFESSOR HEATH. Would you like to see radiographs of the chest taken on October 8, 1977?

PROFESSOR HARRIS. Yes. Well the posteroanterior view of the chest is consistent with pulmonary edema and a small effusion at the right base (Fig. 1). The heart is enlarged and the pulmonary trunk is prominent. There is some calcification in the wall of the aorta which is of normal shape. The more penetrating view shows the outline of the heart more clearly and, although it is difficult to be certain as to which cardiac chamber is enlarged in a straight posteroanterior view I should hazard a guess that it is the left ventricle. The bifurcation of the trachea is not widened, the left atrial appendage is not prominent, and the right border of the left atrium is not visible, which leads me to believe that the left atrium is not enlarged. The lateral view shows no evidence of calcification in the mitral or aortic valves. These views are consistent with my assessment of the clinical story although the enlargement of the pulmonary trunk is more than I would have expected.

PROFESSOR HEATH. Here are three electrocardiograms taken on October 7, 9 and 10, 1977.

PROFESSOR HARRIS. At times there is an irregular rhythm consistent with atrial fibrillation. At other times there are P waves associated with a lengthening of the PR interval consistent with a severe first-degree heart block (Fig. 2). The QRS complexes are abnormally wide. The axis is far over to the left. This implies left bundle branch block. There are many ectopic beats which come from different places in the ventricular wall. I do not think these electrocardiographic changes help distinguish between ischemic and idiopathic cardiomyopathy because, when you have left bundle branch block, the passage of the impulse through the left ventricle is so abnormal that you could miss the likely abnormalities which might be due to ischemic heart disease or the focal changes in the myocardium which might be due to cardiomyopathy. We can, however, say that, whereas the chest radiograph suggested that there is nothing seriously wrong with the mitral valve, the ECG changes suggest that there is something seriously wrong with the myocardium.

DR. MCKENDRICK. Do we know whether this patient had any treatment at all before he came

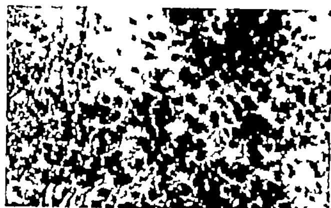


Fig 3 Deposits of amyloid on the endocardial surface of the right atrium stained with iodine.

to the hospital? I think that for a man who was brought in with pulmonary edema and congestive cardiac failure the pulse rate was abnormally slow and so a history of drug ingestion might be relevant.

DR. WILSON In fact I think the apical pulse rate was considerably higher than 100 on admission. He had no previous medication apart from "Franol" tablets.

DR. EVANS Do you think that a cardiac aneurysm might be present here? The left ventricular contour looks rather irregular to me. This would explain the attacks of rhythm disturbance, intractable cardiac failure and possibly through both the loss of consciousness.

PROFESSOR HARRIS I would have thought that in a cardiac aneurysm there is more likely to have been a clear-cut history of an acute myocardial infarction. The shape of the heart shadow is not always entirely helpful in this circumstance because one can have a normal silhouette hiding an aneurysm.

PROFESSOR HEATH It is becoming more and more apparent that there are some diseases which are characteristic of the aged heart. One example is calcification of the mitral valve annulus which gives rise to characteristic clinical and radiographic features. Do you think that there is any disease characteristic of the aged heart which could account for the cardiomyopathy which you have diagnosed in this case?

PROFESSOR HARRIS My own view would be that increasing age has its main effect by increasing the incidence of the likelihood of ischemic heart disease.

PROFESSOR HEATH Well let us ask Dr Cruickshank what he found at necropsy



Fig. 4. Deposits of amyloid on the epicardial surface of the right ventricle stained with iodine.

DR. CRUICKSHANK It was possible to make the diagnosis of this case in the postmortem room. The heart was big, weighing 691 g. Both ventricles were enlarged the left weighing 467 g (normal up to 185 g) and the right weighing 112 g (normal up to 65 g) The coronary arteries were normal showing only trivial atheroma. There was no fibrosis of the myocardium. The endocardial surfaces of both atria showed numerous translucent or greyish pin head nodules. They were most striking in the inferior vena cava. These nodules assumed a deep mahogony brown color with iodine, thus indicating that they were amyloid (Fig. 3) Deposits of amyloid were also seen on the epicardial surface of the heart and on the endocardial surface of the right ventricle (Fig. 4). This was without doubt a case of primary amyloid disease of the heart. Thus the widespread damage of the myocardium predicted by Professor Harris turned out to be due to deposits of amyloid. The other organs showed features of congestive cardiac failure.

Histological examination confirmed the presence of amyloid The deposits of amyloid stained



Fig. 5. Dichroic reaction of nodule of amyloid seen in a histological section of tissue from the wall of the right atrium.

with Congo Red. Sections stained with this dye gave a dichroic reaction with polarized light, the typical apple-green birefringence being given (Fig. 5). A dichroic reaction was also given with deposits stained with Sirius Red. Sections stained with hematoxylin and eosin showed the characteristic apparently amorphous deposits in the myocardium as well as in the endocardium (Fig. 6). Sections treated with Thioflavine T showed the characteristic fluorescence with ultraviolet light. In most of the other organs amyloid was most conspicuous in the veins. This was seen in the pancreas, the adrenal, the thyroid, and the prostate. There was diffuse amyloid in the lung. There is an inherited form of amyloid disease described in Portugal in which the amyloid is laid down in the nerves, the so-called familial amyloid neuropathy. In the present case I found only one small nodule of amyloid deposition in one nerve so it does not represent an example of this form of the disease. So this was a case of primary amyloidosis of the heart with other deposition of amyloid in the veins throughout the body.

PROFESSOR HEATH. Mr Biggar you have made a special histochemical study of amyloid, would you like to make one or two comments about dichroism?

MR. BIGGAR. When amyloid is stained up by Congo Red the longitudinal axis of the Congo Red molecule lies parallel with the longitudinal amyloid fibrils, and this arrangement between the two is said to produce a pseudocrystalline structure. When the stained section is examined under polarized light and when the plane of polarized light is parallel with the Congo Red molecule and

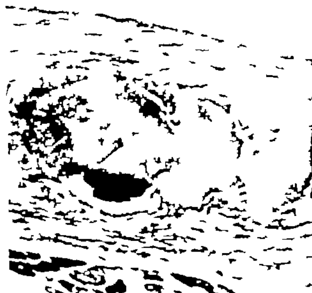


Fig. 6. Histological section of deposit of amyloid in the endocardium of the right atrium stained with hematoxylin and eosin. The apparently amorphous appearance of the amyloid belies its complex fibrillar composition demonstrated on electron microscopy.

the amyloid fibril, red light is absorbed and the apple-green birefringence is produced. If the plane of polarized light is not parallel with the long axis of the Congo Red, golden yellow birefringence is produced and the combination of these two colors is known as dichroism.

PROFESSOR HEATH. That sounds like a good question for the examination in Pathology for the medical students. (Laughter) With the aging population of Britain we are increasingly becoming aware of diseases which are characteristic of the aged heart. Such a condition is the deposition of amyloid in the hearts of those over 70 years and even more so in the hearts of those over the age of 80 years. How many cases have the Cardiologists present seen in which amyloid deposition in the heart has been so severe as to lead to such clinical signs and symptoms as in the present case?

PROFESSOR HARRIS. I have seen two such cases before today.

DR. MCKENDRICK. In 20 years practice I have seen two such cases but both of them died very slowly in chronic congestive heart failure in contrast to the acute manner of the death in this case. In both, the amyloid was confined to the heart, although I don't know if the Pathologists at that time looked for amyloid so carefully in the systemic veins as they do nowadays and in the present case.

PROFESSOR HEATH Do you think that Cardiologists have primary amyloidosis of the heart in their diagnostic repertoire for elderly patients? Are they familiar enough with the condition, or do you think that it is genuinely a very rare condition?

PROFESSOR HARRIS I think it is genuinely a very rare condition, because after all it is a killing condition, and this being the case most of these cases would go to necropsy where their true nature would become apparent.

DR. WHITWELL I agree that primary amyloid disease of the heart, presenting as congestive heart failure, is extremely rare. In my practice as a Pathologist I have seen only four cases in 25 years. This is in contrast to calcification of the mitral ring, which is commonplace in the aged.

Diagnosis Primary amyloid disease of the heart.

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Fundamentals of clinical cardiology

Rationale and use of vasodilators in the management of congestive heart failure

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Burch's initial description of hexamethonium for the relief of intractable ventricular dysfunction was largely ignored until recently when a land slide of literary material has emerged proclaiming the effects of vasodilator therapy in the management of patients with congestive heart failure. Several comprehensive reviews of vasodilator therapy have been published. Nevertheless, a number of areas concerning this therapy remain clouded. In this presentation, we attempt to synthesize the results of numerous investigations and reviews into a form that may assist in the evaluation of this therapy.

Physiological considerations

In patients with depressed left ventricular performance, reflex systemic vasoconstriction may lead to a further reduction of cardiac output[1] by placing an added load on the ventricle. These patients respond differently from normals to a reduction of systemic resistance. In normal subjects a decrease in peripheral resistance results in a compensatory reflex tachycardia. This reflex tachycardia is attenuated in patients with congestive cardiac failure, when a reduction of peripheral resistance is accompanied by an increase in stroke volume without an increase in heart rate.[4] Arterial pressure, therefore, is maintained by the increase in stroke volume.

Following the administration of systemic vasodilators the reason that stroke volume increases, in our judgment, must be related to a transient reduction of arterial pressure. This transiently decreased pressure lowers the ventricular afterload (wall tension) which permits greater shortening of muscle fibers. The augmented stroke volume results in a return of blood pressure to near control level. The increased fiber shortening, once initiated, will be maintained. Since tension relates to pressure × radius, a momentary reduction of pressure will transiently diminish the ventricular wall tension during ejection. As myocardial tension defines the afterload in the heart, afterload is reduced. In this sense vasodilatation causes a reduction of afterload. The reduced afterload, according to tenets of muscle mechanics, will permit a greater rate and extent of contraction. Stroke volume is, therefore, augmented. The beneficial effects resulting from a drug induced arterial dilatation in congestive heart failure include increased stroke volume, decreased end-systolic volume, decreased myocardial wall tension, and increased work and power of contraction. To some extent, greater myocardial efficiency may result.

Vasodilators may also have a dilating effect upon the veins, thereby increasing the blood volume in the venous bed and decreasing venous return. This leads to a reduction of ventricular diastolic pressure and a reduction of overstretch of myocardial fibers, allowing more efficient contraction. The heart contracts from a smaller end-diastolic volume permitting contraction with less myocardial tension[14] (tension equals pressure × radius). This reduced tension leads to increased efficiency (ratio of useful work to

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myocardial oxygen consumption) Decreased diastolic tension may reduce intramyocardial pressure and subendocardial coronary resistance thereby increasing subendocardial coronary flow allowing a more favorable distribution of flow However coronary driving pressure may also decrease. In dogs with congestive heart failure, in spite of a reduced pressure increased subendocardial blood flow to ischemic myocardium was observed with vasodilator drugs. Thus, a series of useful physiological events result from decreased venous return in the distended and failing heart.

We believe that the above mechanisms can reasonably explain the beneficial effects of vasodilator drugs in congestive heart failure Several terms, however have been used in the literature with different definitions. This results in clouding the mechanism of action of these drugs, and causes unnecessary complexity in the thoughtful evaluation of this form of therapy

Definitions

1 **Afterload** Afterload, in isolated muscle bundle studies, refers to the additional load (beyond the load required for initial stretch) against which a muscle contracts. Thus, after load means tension (force) [11] Problems in the application of this term to the intact heart result. To be strictly analogous, afterload of the intact heart should be defined as tension developed in the ventricular wall as contraction occurs. This definition has been suggested by some who have investigated muscle mechanics.

The tension developed during contraction relates to intraventricular pressure ventricular diameter and wall thickness through the LaPlace equation As these vary afterload (wall tension) is difficult to measure Since afterload is determined by aortic pressure among other variables, aortic pressure is sometimes referred to as afterload. Milnor[1] defines afterload as the input impedance spectrum of the ascending aorta

2 **Impedance** Impedance is computed as the ratio of sinusoidal pressure to sinusoidal flow at the same frequency and is the measure of the opposition to flow presented by a system With steady flow in rigid tubes impedance is identical to resistance (pressure divided by flow) With pulsatile flow in the presence of expansile vessels, peak flow occurs before peak pressure The measurement of impedance requires the simultaneous measurement of phasic pressure and flow and the determination of the frequency content of both signals by Fourier analysis. Impedance is an advantageous measurement because it provides information related to arterial compliance, reflected waves, vessel dimensions, and viscosity Resistance gives information related only to vessel dimensions and viscosity Thus, impedance relates more information, but is complex in its computation. Although reference is made to impedance, in fact *resistance* is generally measured and described.

3 **Preload** In isolated muscle preparations, preload refers to the load that establishes the resting length of the muscle. In the intact heart, preload should thus refer to end-diastolic ventricular wall tension, but is generally equated with left ventricular filling pressure or left ventricular end-diastolic pressure.

Therapy of congestive heart failure

Conventional therapy for patients with congestive heart failure is directed at reducing the work load on the heart (bed rest) improving myocardial function (digitalis) and decreasing fluid overload (diuretics and sodium restriction) Obviously any treatable underlying cause for the heart failure requires management. Although these measures remain the mainstay of therapy administration of vasodilator agents has been found to result in improvement of congestive heart failure of diverse etiologies. In the acute situation, especially following myocardial infarction, careful hemodynamic monitoring is advisable to avoid marked fluctuations of arterial pressure which may occur if there is fluid depletion or if the infusion rate of vasodilator agents is too rapid.

Vasodilator agents

A number of vasodilator agents have now been used in the management of various conditions in order to reduce left ventricular end-diastolic pressure and peripheral vascular resistance. A review of these agents and their mechanism of action has been recently published by Chatterjee and Parmley The vasodilator agents in use are summarized in Table I. The major sites of action, mode of administration, and duration are tabulated. It should be noted that some of the vasodilators can only be used by parenteral administration. These

Table I

Drugs	Mode of administration	References	Duration of action	Predominant site of action
Phentolamine	Continuous intravenous infusion	17 23	Minutes	Arterial
Trimethaphan	Continuous intravenous infusion	24	Minutes	Arterial and venous
Nitroprusside	Continuous intravenous	25-34	Minutes	Arterial and venous
Nitroglycerin	Continuous intravenous	33,35	Minutes	Venous
Nitroglycerin	Sublingual	43-44	20-30 Minutes	Venous
Nitroglycerin	Ointment	47-41	3-5 Hours	Venous
Isosorbide	Sublingual	45,46	60-90 Minutes	Venous
Dinitrate	Oral	51-54	± 4½ hours	Venous
Phenoxybenzamine	Oral	59	± 4-6 Hours	Arterial
Hydralazine	Oral	55,56	± 6 Hours	Arterial
Prazosin	Oral	60-63	± 6 Hours	Arterial and venous

include phentolamine, [23] trimethaphan,[24] sodium nitroprusside,[25-34] and intravenous nitroglycerin.[33, 35] This limits their usefulness to acute situations, preferably where continuous hemodynamic monitoring is possible. The two drugs that have been studied most extensively are sodium nitroprusside and nitroglycerin. Their mechanism of action differs in that sodium nitroprusside results in dilatation of both the arterial and venous vessels,[27 38] whereas nitroglycerin, as do the other nitrites, has its major effect upon the veins.[39-42]

The drugs that are administered sublingually (sublingual nitroglycerin[43-44] and sublingual isosorbide dinitrate[45 46]) have a relatively short duration of action and initially may produce hypotension. Consequently starting doses should be low and frequent administration which often is impractical, is necessary for continued action. A longer effect (3 to 6 hours) has been achieved using nitroglycerin as an ointment. [47] Prolonged daily use, however is limited because of the problems of application. Orally administered agents such as oral isosorbide dinitrate[51 54] and hydralazine[55, 56] have a longer duration of action (approximately 4 and 6 hours, respectively) and are more practical. Orally administered isosorbide dinitrate has its primary effect upon the capacitance vessels (veins) and results in only a modest increase in cardiac output. Its use may thus be limited in patients with low output congestive heart failure in whom the primary objective would be to increase cardiac output. Hydralazine, on the other hand, has its major action on the resistance vessels (arteries) and a striking increase in cardiac output as well as a reduction in systemic and pulmonary vascular resistance has been documented.[55, 56] In the presence of congestive cardiac failure, unlike the usual response in patients with compensated systemic hypertension, hydralzine does not result in a significantly increased heart rate.[56] Because hydralazine does not cause marked dilatation of the capacitance vessels, pulmonary wedge pressure may remain elevated with persistent symptoms of pulmonary venous congestion. Under these circumstances, concomitant use of a diuretic or long-acting nitrate,[57] may produce improvement. Patients receiving hydralazine therapy for hypertension in dosages of 200 mgm. per day have developed a lupus-like syndrome.[58] Whether this will limit the usefulness of hydralazine in patients with congestive heart failure still requires assessment. Encouraging results were also obtained in four of 12 patients with chronic congestive cardiac failure treated for 3 to 21 months (mean 7 months) with a combination of the alpha blocking agent phenoxybenzamine and sublingual isosorbide dinitrate.[59]

More recently prazosin, a vasodilator which has effects on both the venous and arteriolar systems, has been used.[60-63] Its acute effects on the circulatory system result in a reduction of both preload and afterload with a consequent reduction of myocardial oxygen requirements.[64] We have found continued clinical benefit with chronic administration. Orthostatic hypotension has not been a problem in our experience. Howev

er the development of rapid tachyphylaxis with prazosin (72 to 96 hours) has recently been reported and this may limit its long term efficacy.[4-6]

Clinical use of vasodilator agents

Since the appreciation that vasodilators could "unload" the heart by reducing preload and/or afterload, many cardiac conditions have been reported in which vasodilator agents were used in the management of patients. Initial reports were almost exclusively directed to their use in the acute phase of myocardial infarction. Subsequently various load reducing drugs have been used to treat patients with congestive heart failure of diverse etiologies ranging from mitral or aortic regurgitation to congestive cardiomyopathies.

Management of acute congestive cardiac failure following myocardial infarction

Studies in dogs demonstrated that regional myocardial ischemia could be alleviated by medical interventions.[46] Drugs that increased myocardial oxygen consumption tended to increase the extent of tissue damage following experimentally induced myocardial infarction.[47] This included inotropic agents such as isoproterenol and ouabain, agents that were previously accepted as [ro]utine therapy in the management of the patient [wi]th myocardial infarction. Once it became [a]pparent that an increase in cardiac performance could be achieved by reducing preload and afterload with a concomitant reduction in myocardial oxygen consumption, vasodilator agents were introduced for the treatment of patients with acute myocardial infarction frequently replacing the need for inotropic drugs. The beneficial effects of vasodilator therapy are most apparent in patients with an elevated left ventricular filling pressure. By their action on the resistance and capacitance vessels they reduce systemic impedance and decrease venous return to the left ventricle. It was also demonstrated that in the presence of an elevated ventricular filling pressure systolic arterial pressure can be maintained. In the patient with acute myocardial infarction, because of the instability of the conditi[o]n arterial and pulmonary wedge pressure should be monitored during vasodilator therapy. The most suitable agents in this situation are those with a rapid onset and a rapid termination of action so that the dosage can be titrated. Several of the intravenously administered agents fulfill these criteria (Table I). Nitroprusside is probably the most widely used[48-54] and has been shown to result in a rapid improvement of cardiac output and a decrease in raised pulmonary wedge pressure, with little change in heart rate. Since toxic blood levels of thiocyanate (75 to 100 mgm./100 mm.)[55] have been reported with continued use of sodium nitroprusside it is recommended that this agent be discontinued after 72 hours. In addition to the functional benefit achieved by the use of these agents, there is evidence to suggest that the early mortality following acute myocardial infarction is improved.[56] However long term follow-up of those patients who were maintained on vasodilator therapy (sublingual isosorbide dinitrate) following discharge from hospital, was disappointing with a projected 2 year survival rate of only 28 per cent.[58]

Mitral regurgitation

Several studies have now shown benefit in the management of acute mitral regurgitation with vasodilator agents.[70-] In patients with mitral regurgitation the ventricle in addition to ejecting blood into the relatively high resistance systemic vascular bed ejects a variable volume, depending upon the severity of the lesion, into the relatively low resistance left atrium. An increase in systemic vascular resistance will increase the severity of mitral regurgitation.[75, 76] In contrast, a reduction of peripheral vascular resistance in patients with severe mitral regurgitation by vasodilator agents augments forward flow and at the same time reduces the amount of regurgitation.[76, 77] Probably several factors act in concert to achieve this result. First, the reduced arterial resistance will permit the ejection of a greater volume of blood into the aorta relative to the left atrium. Secondly those drugs which affect the capacitance vessels cause a decrease in venous return to the right heart and ultimately to the left atrium. A reduced regurgitant volume together with a reduction in pulmonary venous return result in a reduction in left ventricular filling pressure, and in the volume of the overloaded ventricle, with a consequent decrease in ventricular size. In patients in whom ventricular dilatation is the mechanism responsible for the mitral regurgitation realignment of papillary muscles may be important in contributing to their improvement. However even in patients with mitral regurgita-

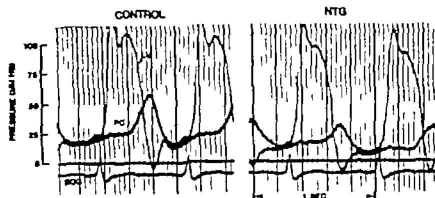


Fig. 1. Left ventricular (LV) and pulmonary capillary (PC) pressures in patient with severe mitral regurgitation during control measurements *(left)* and five minutes after the sublingual administration of nitroglycerin *(right)* 0.4 mgm.

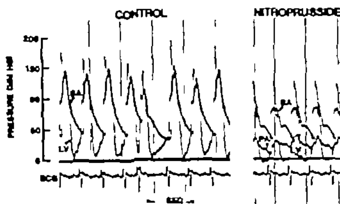


Fig. 2. Brachial arterial *(BA)* and left ventricular *(LV)* pressures in patient with severe aortic regurgitation during control measurements *(left)* and the administration of nitroprusside *(right)*. Pulmonary arterial *(PA)* pressure was also recorded during nitroprusside infusion.

tion secondary to chronic rheumatic mitral valve disease, significant improvement has been demonstrated in the degree of regurgitation with the use of vasodilator therapy.[71, 72] A reduction in subendocardial ischemia secondary to a reduced filling pressure, reduced ventricular cavity size, and reduced diastolic wall stress[73] also contribute to improved myocardial function.

To date only the effects of acutely administered vasodilator agents have been studied in patients with mitral regurgitation (Fig. 1). Long term therapy with longer acting agents theoretically could have marked beneficial effects for those patients with mitral regurgitation where surgery is not practical or the mitral regurgitation is secondary to a cardiomyopathic ventricle.

Aortic regurgitation

In general, symptomatic aortic regurgitation is an indication for surgical intervention. Although a beneficial response has been achieved in some patients with a decreased cardiac output, elevated left ventricular end-diastolic pressure, and reduced ejection fraction using vasodilators,[77] long term results of management of these patients are not available. In those situations where the patient develops acute aortic regurgitation, vasodilator therapy can be a lifesaving temporizing measure until surgery can be undertaken (Fig. 2).

Ventricular septal defect

A relatively uncommon, but dramatic complication of acute myocardial infarction is rupture of the interventricular septum. These patients usually develop acute congestive cardiac failure secondary to the left-to-right intracardiac shunt at the ventricular level. As the development of the interventricular septal defect is acute, compensatory mechanisms in the pulmonary

vascular bed cannot occur The pulmonary vascular resistance in these patients is usually low with high flows and consequently a large volume overload.[78] Operation in the acute phase of the illness has been associated with a high mortality rate[79] and improved results have been obtained if surgery can be delayed for 6 weeks or longer.[80, 81] Vasodilator therapy during the acute phase in dogs with experimentally induced ventricular septal defect has been shown to be of benefit in the management of the left ventricular failure.[82] Vasodilator therapy in patients with an acute ventricular septal defect following myocardial infarction together with routine anti failure therapy may well permit postponement of surgery until surgical repair can be conducted under more favorable circumstances.

Chronic congestive cardiac failure

A number of reports have focused attention on the management of patients with chronic congestive cardiac failure following myocardial infarction or in patients who have refractory failure and in whom surgery is not indicated.[84, 85, 86, 87]

In a study of 10 patients with chronic congestive cardiac failure using hydralazine, Chatterjee and associates[84] found that cardiac output increased in all, and seven of the nine patients improved to New York Heart Association Class II (six were NYHA Class IV and one was NYHA Class III prior to their being administered hydralazine). Awan and colleagues[87] found similar beneficial effects in nine patients using prazosin. This agent has an effect on both capacitance and resistance systems and has been shown to decrease pulmonary venous pressure and at the same time to increase cardiac output. The combined use of long acting nitrates and hydralazine for the management of chronic congestive cardiac failure has also proved beneficial.[34]

Vasodilators have now found a place in the clinician's therapeutic armamentarium. Used alone or in combination with conventional therapy or inotropic agents, improvement in myocardial performance is possible in the majority of patients with congestive heart failure.

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ppraisal and reappraisal of cardiac therapy

dited by Arthur C DeGraff and Julian Frieden

he role of physical training in patients with coronary artery disease

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Interest in the role of physical fitness and training in the prevention and treatment of coronary artery disease has increased over recent years. Multiple symposia,[1-] review papers, and monographs[-] have appeared on this subject. The scene of joggers in the streets and parks has become common, and the enrollment in medically supervised exercise programs has increased. The favorable effect of physical training on improvement of cardiovascular function is well documented. However many of those engaged in a regular exercise program hope not only to improve cardiovascular fitness, but also to prevent or attenuate the risks of atherosclerotic coronary disease, specifically myocardial infarction and death. Unfortunately the studies on the effect of sustained exercise on longevity and reinfarction are equivocal. Thus, because of the uncertain role of physical training in either the prevention or treatment of coronary artery disease, as well as the potential risks and costs, exercise therapy has become a highly controversial issue. This review will discuss the physiologic effects of exercise in patients with coronary artery disease and its role in treatment.

Prophylactic value of exercise in the prevention of coronary artery disease

Anecdotal experiences are often cited as examples of the beneficial effects of physical training.

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†Dr Arbeit died on July 21, 1978.

The autopsy findings of the famous runner Clarence DeMar who continued long distance running until his death at the age of 70, typifies these reports.[11] On postmortem examination, the coronary arteries were two to three times normal size with only non-obstructive atherosclerotic involvement. One might conclude that the many years of long distance running had resulted in enlarged coronary arteries. However an equally plausible conclusion would be that DeMar had become a great runner because of a genetic predisposition to large coronary arteries. Bassler [12] based on his extensive observations of autopsy results, has claimed that marathon runners are completely immune to fatal atherosclerosis. Others have refuted this as an exaggerated claim by documenting cases of fatal myocardial infarction in marathon runners and by emphasizing that self-selection and other variables such as diet and smoking habits must be considered in evaluating the "protective effect of long distance running.

Population studies have been done to decide whether exercise might be effective prophylaxis against coronary artery disease. The classic work by Morris and associates[13] demonstrated a decreased incidence in both the frequency and severity of myocardial infarction in civil servants with more physically active jobs (bus conductors) as compared to more sedentary workers (bus drivers). These findings seemingly support a role for physical activity in the prevention of coronary artery disease. However Morris and co-workers[1] published additional data 3 years later and noted that the sedentary drivers had both a greater girth and weight prior to employment than the more active conductors, thus raising the *question*

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of self-selection and personal preference of more obese workers—already at greater risk for the development of coronary artery disease—for the sedentary jobs.

Other population studies have investigated the risks of cardiac events in physically active population groups compared to sedentary controls in an attempt to establish the possible protective effect of physical activity against cardiac events. Probably the best known of these studies is the work by Paffenbarger[4] who studied the incidence of fatal myocardial infarctions among San Francisco longshoremen. These longshoremen represent a stable population observed over many years with well described workloads as defined by their union contract. The workers were classified into groups according to their workday energy expenditure. The more sedentary longshoremen had an 80 per cent increased risk of fatal myocardial infarction when compared to workers with higher energy output jobs. The work energy output level was either of equal or greater influence in predicting death from coronary disease as other risk factors such as cigarette smoking, hypertension previous known heart disease, obesity and cholesterol. The results of this study are strongly supportive of a protective effect of a lifetime of extremely vigorous physical activity against fatal myocardial infarction and especially against sudden death. Whether a protective effect can also be seen with lesser degrees or different types of physical activity is yet to be shown.

A recent review by Froelicher[5] summarized the multiple epidemiologic studies. He emphasized both the difficulty in differentiating between self-selection and protection and the problems in these population studies in controlling for other risk factors and assessing physical activity from job descriptions and questionnaires. He concluded that although the studies to date are suggestive of a protective effect of physical activity against myocardial ischemic events, the data are not definitive.

Physiologic concepts—definition of terms

The physiologic effects of physical training have been studied in both normal subjects and in patients with symptomatic coronary artery disease. The terms physical training, exercise training, and physical conditioning will be used interchangeably in this paper to refer to repetitive isotonic muscular exercise carried out on a regular basis for the purpose of improving an individual's ability to perform a specific task.

The amount of aerobic work which the body performs can be measured in terms of oxygen consumption (VO_2). The more work an individual performs, the higher will be his energy demand and therefore the greater the amount of oxygen consumed. Different tasks which require the same oxygen consumption can be compared. For example, a 70 kilogram man, walking on a treadmill at 1.7 miles/hour at a 10 per cent grade would expend approximately 14 c.c. O_2/Kg./minute which is the same oxygen expenditure for swimming at 20 yards/minute. The energy demand for a variety of submaximal tasks can thus be quantified in terms of oxygen consumption.

With increasing energy expenditures, there is a normal increase in heart rate, blood pressure, and cardiac output. As the body reaches its maximum ability to consume oxygen (VO_2 max), there is a leveling off of the blood pressure and pulse rate with increased load. The maximum oxygen consumption is a reproducible measure of one's work capacity or state of physical fitness. Values for VO_2 max may range from 24 c.c./Kg./minute in sedentary middle-aged individuals to values as high as 80 c.c./Kg./minute in highly trained individuals. Thus the state of physical fitness and improvement in physical fitness are quantifiable. In addition to the state of physical training, other factors such as age, sex, and underlying disease processes are determinants of VO_2 max.

Patients with coronary artery disease have an additional limitation to their exercise capacity in that the diseased coronary circulation cannot keep up with the increased myocardial oxygen demand during exercise. Such patients will develop myocardial ischemia before their theoretical VO_2 max. and stop exercise because of angina. This endpoint is referred to as the symptom-limited oxygen consumption (VO_2 sl). Exercise in patients with coronary artery disease can also induce left ventricular dysfunction, as demonstrated by elevation in left ventricular end-diastolic pressure (LVEDP) or reduction of stroke volume without chest pain. Thus the response of patients with coronary disease to exercise can be limited not only by symptoms of angina but also by extreme dyspnea or fatigue. An additional endpoint is the development of ventricular arrhythmias, possibly secondary to myocardial ischemia or left ventricular failure.

An important objective of a physical training

Table I Physiologic determinants and clinical correlates of myocardial oxygen demand and supply

	Myocardial oxygen demand	Myocardial oxygen supply
Physiologic determinants	Left ventricular wall tension Myocardial contractility Heart rate	Coronary blood flow Myocardial oxygen extraction Transmural diastolic pressure gradient (aortic diastolic pressure—left ventricular diastolic pressure) Duration of diastole Regional distribution of myocardial blood flow
Clinical correlates	Rate pressure product = heart rate × mean arterial pressure Double product = heart rate × systolic blood pressure Triple product = heart rate × systolic blood pressure × systolic ejection time Tension-time index = heart rate × integral of left ventricular pressure during systole	Maximal rate pressure product, double product, triple product or tension-time index achieved at time of angina Aortic diastolic pressure × time—ventricular diastolic pressure × time

program in patients limited by coronary artery disease is to train the body to perform a given amount of work with less demand for the limited myocardial oxygen supply. The major determinants of myocardial oxygen demand are heart rate, wall tension, and contractility (Table I). In the clinical assessment of patients with angina pectoris, the product of heart rate and mean blood pressure (rate–pressure product or RPP) is used as an index of myocardial oxygen demand. Other indices such as the double product, triple product, and tension time index have also been used (Table I). Robinson has demonstrated that in patients with stable angina chest pain occurs at a reproducible RPP. It has further been shown that the RPP at anginal threshold is the same regardless of the type of stress provoking the angina. Hence an improvement in exercise capacity can be brought about by reducing the rate pressure product and therefore the myocardial oxygen demand for a given task. If an individual can exercise to a higher rate pressure product before experiencing angina, it is implied that he has increased his myocardial oxygen supply.

Effects of exercise training

Maximum exercise. Although normal physical activities do not call for maximal exertion, physical fitness is quantified in terms of the maximum work capacity. A consistent effect of physical training is to increase the work capacity as measured by VO_2 max. The amount of increase in VO_2 max depends both on the pretraining level of fitness and the intensity and duration of exercise. Studies by Detry and colleagues,[19] Redwood and associates,[20] and others[7, 11] have shown that patients with coronary artery disease can increase their maximum oxygen consumption. The mechanism by which VO_2 max is increased is different in coronary patients from that in healthy individuals. Oxygen consumption is dependent on the product of cardiac output and arterial venous oxygen difference. While normal subjects increase VO_2 max by increasing both the maximal cardiac output and the maximum arterial–venous oxygen extraction ($A–VO_2$), coronary patients increase only the maximal $A–VO_2$.[21] The predominant mechanism for this increase in $A–VO_2$ is an increase in oxygen extraction by the peripheral muscle thought to be due to mitochondrial and enzyme changes in the trained skeletal muscle. Hence, the increase in maximal work capacity in cardiac patients is primarily due to the effect of exercise on the trained peripheral muscles. Physical training does not usually alter the maximum attainable heart rate; however some patients previously limited by angina are capable of exercising to higher heart rates following exercise training.[19, 20]

Submaximal exercise. Daily activities require only submaximal levels of exertion and therefore the benefit of conditioning to patients should also be evaluated during submaximal exercise. The absolute oxygen consumption required to perform a specific submaximal work load is not altered by physical training except insofar as repetition of a particular task facilitates more efficient performance of that task. As the maxi

mal work capacity (VO_2 max) is increased with training, however a specific submaximal work load represents a lower relative percentage of VO_2 max. Changes in heart rate as well as the degree of vasoconstriction in visceral vascular beds is proportional to this relative oxygen demand.[illegible] Following a period of physical training, individuals have a slower resting pulse and a lower heart rate and blood pressure response to exercise. The rate pressure product and therefore the myocardial oxygen demand are reduced during submaximal exercise. This lower heart rate at submaximal exercise has been shown by Varnauskas[illegible] to be accompanied by a rise in the systemic arterial venous oxygen difference. As demonstrated with maximal exercise, during submaximal exercise trained muscles are better able to extract oxygen and maintain oxygen consumption at a reduced muscle blood flow. Clausen and Trap-Jensen[illegible] have shown that after training, both cardiac output and muscle blood flow are reduced during submaximal exercise as compared to pre-training values, and that there is a redistribution of blood flow to the visceral organs. Moreover, the usual rise in peripheral lactate levels during submaximal exercise is attenuated after training, implying more rapid and efficient oxidation in the peripheral muscle cells.[illegible] Letac and co-workers[illegible] have demonstrated by comparative hemodynamic and angiographic studies in patients with coronary artery disease that physical training does not directly affect resting myocardial contractility as measured by ejection fraction, segmental contractility or velocity of circumferential fiber shortening. Although these studies do not preclude changes in myocardial contractility that may occur during stress, the lack of a direct influence of physical conditioning on the myocardium further supports the importance of changes in the peripheral skeletal muscles.

In summary, therefore, following a period of physical training, patients with coronary artery disease can exercise to the same submaximal work load with a slower heart rate, a decreased rate pressure product, and therefore a decrease in myocardial oxygen demand. Local changes in the trained skeletal muscles are primarily responsible for this decrease in myocardial work.

Myocardial oxygen supply—demand ratio

A major beneficial effect of physical training in patients with coronary artery disease would be alteration of the myocardial oxygen supply–demand relationship. The indirect indices of myocardial oxygen demand (rate pressure product, double product and others) are often used to examine this relationship. The effect of physical training in reducing the indirect indices of myocardial oxygen consumption has been discussed in detail above. Several studies have shown that not only is the RPP decreased at any specified submaximal workload, but that a group of patients can exercise to a higher rate pressure product (or triple product) before angina or exercise to exhaustion without angina.[illegible] This implies either an increased myocardial oxygen supply or a decrease in a determinant of oxygen demand not measured by RPP. A recent study of the effect of physical training on coronary sinus blood flow in patients with angina pectoris demonstrated that the decrease in heart rate and rate-pressure product which occurs during submaximal exercise after training is accompanied by a decrease in coronary blood flow.[illegible] The coronary blood flow during maximal exercise was not significantly changed after training. A group of patients, however, was able to increase both the maximum rate pressure product and coronary sinus blood flow at the onset of angina, implying that at least a subgroup of patients may have increased myocardial oxygen supply after training. Although a study by Sim and Neill[illegible] demonstrated an increased triple product to angina when tested by exercise on a bicycle ergometer, there was no change in anginal threshold when tested by atrial pacing. This suggests that conditioning might possibly alter the relationship between actual MVO_2 and the indices by which it is often measured (RPP, triple product). A study by Detry and Bruce,[illegible] which demonstrated an increased RPP threshold to angina after training, found that training did not alter the relationship between ST segment depression and rate pressure product. Thus although the RPP at the time of angina was higher, so was the extent of ST segment depression, raising the possibility that training altered the relationship between angina and myocardial ischemia as measured by ST segment depression.

Because of the high myocardial oxygen extraction in the basal state (approximately 70 per cent compared to 20 per cent in the systemic circulation), increased myocardial oxygen needs must usually be met by increased coronary blood flow. The transmural myocardial blood flow is dependent on the difference between the aortic and left

Table II Physiologic effects of physical training in patients with coronary disease

	Parameter	Effect of training
I	*Measured during maximal exercise*	
	Work capacity	Increased
	Maximum oxygen uptake (VO_2 max) or symptom limited oxygen uptake (VO_2 sl)	Increased
	Maximum heart rate	Increased or no change
	Maximum A-VO_2 difference	Increased
	Maximum cardiac output	Decreased or no change
	Maximum double product, triple product or tension time index at time of angina	Increased or no change
II	*Measured during exercise at specified submaximal work loads*	
	Oxygen uptake	No change
	Heart rate	Decreased
	Stroke volume	Variable effects
	Cardiac output	No change or decreased
	A-VO difference	Increased
	Blood pressure	No change or decreased
	Double product, triple product, tension-time index	Decreased
III	*Measured at rest*	
	Heart rate	No change or decreased
	Blood pressure	No change or decreased

Table III Comparison of various interventions in the treatment of angina

Intervention	Rate pressure product (RPP) at specified submaximal work load (myocardial oxygen demand)	Maximum rate pressure product at time of angina (myocardial oxygen supply)
Nitroglycerin	Decreased	No change or increased
Propranolol	Decreased	N change or decreased
Coronary artery bypass surgery	No change	Increased
Physical training	Decreased	No change or increased

ventricular diastolic pressures and the duration of diastole. Relative bradycardia induced by exercise training prolongs diastole and allows for increased coronary filling. In patients with fixed obstructive coronary artery disease, the ability to increase coronary blood flow with increased demand is severely limited. Collateral coronary vessels may potentially serve to increase blood flow to ischemic areas of myocardium. Although some studies have shown increased vascularity in rats after training and increased collateral flow in dogs, none of the studies in man with coronary artery disease has shown increased collateral circulation resulting from a physical training program.[13, 22, 23, 24] This may be due to the fact that (1) coronary angiograms are done at rest, (2) the collateral vessels may be too small to visualize on coronary angiograms, (3) the duration of training necessary to produce an increased collateral circulation might have to be longer than that performed in these studies, or (4) there is no increase in collateral vessels in man. Thus the evidence that exercise training improves myocardial oxygen supply is indirect and inconclusive.

The physiologic effects of physical training in patients with coronary artery disease are summarized in Table II. In addition to these hemodynamic effects, other beneficial effects on coronary risk factors such as decreased weight, decreased serum triglycerides and free fatty acids,[17] and improved glucose tolerance have been observed.[14] Moreover psychological changes such as increased self-confidence, and reduced depression and hypochondriasis have been reported.[24]

Comparison of physical training, nitroglycerin, and propranolol

As shown in Table III, different modalities for the treatment of angina have varying effects on myocardial oxygen supply and demand. Both

mal work capacity (VO_2 max) is increased with training, however a specific submaximal work load represents a lower relative percentage of VO_2 max. Changes in heart rate as well as the degree of vasoconstriction in visceral vascular beds is proportional to this *relative* oxygen demand.[illegible] *Following a period of physical training*, individuals have a *slower resting* pulse and a lower heart rate and blood pressure response to exercise. The rate pressure product and therefore the myocardial oxygen demand are reduced during submaximal exercise. This lower heart rate at submaximal exercise has been shown by Varnauskas[illegible] to be accompanied by a rise in the systemic arterial venous oxygen difference. As demonstrated with maximal exercise, during submaximal exercise trained muscles are better able to extract oxygen and maintain oxygen consumption at a reduced muscle blood flow. Clausen and Trap-Jensen[illegible] have shown that after training, both cardiac output and muscle blood flow are reduced during submaximal exercise as compared to pre-training values, and that there is a redistribution of blood flow to the visceral organs. Moreover, the usual rise in peripheral lactate levels during submaximal exercise is attenuated after training, implying more rapid and efficient oxidation in the peripheral muscle cells.[illegible] Letac and co-workers[illegible] have demonstrated by comparative hemodynamic and angiographic studies in patients with coronary artery disease that physical training does not directly affect resting myocardial contractility as measured by ejection fraction, segmental contractility or velocity of circumferential fiber shortening. Although these studies do not preclude changes in myocardial contractility that may occur during stress, the lack of a direct influence of physical conditioning on the myocardium further supports the importance of changes in the peripheral skeletal muscles.

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Comparison of physical training, nitroglycerin and propranolol

As shown in Table III, different mo F the treatment of angina have varying myocardial oxygen supply and

nitroglycerin and physical training have similar effects in terms of decreasing the double product at specific submaximal workloads. While physical training primarily decreases the heart rate during submaximal exercise nitroglycerin decreases the blood pressure and may often actually increase the heart rate though the RPP remains lower Both physical training and nitroglycerin may increase the double product at the anginal threshold in certain patients.[19, 20, 21]

Beta adrenergic blockade, like physical training, reduces myocardial oxygen consumption during submaximal exercise by reducing heart rate and blood pressure, and thus *increases* the exercise capacity Propranolol however may cause a *decrease* in maximal heart rate and maximal rate pressure product at the time of onset of angina.[20] The decreased anginal threshold values for heart rate and RPP following β blockade may be related to an elevated left ventricular diastolic volume with its increased wall tension and myocardial oxygen demand (Table I) As emphasized by Clausen [22] although both propranolol and physical training blunt the heart rate and blood pressure responses to specific submaximal workloads, the mechanism of action is different. Physical training causes a decrease in sympathetic stimulation to the heart and a redistribution of blood flow to non-exercising tissue and more efficient oxygen utilization by exercising muscle Beta blockade on the other hand, prevents the heart from responding to increased sympathetic stimuli, and results in α induced peripheral vasoconstriction and decreased blood supply to the visceral organs.

Coronary artery bypass surgery results in increased blood supply to the myocardium and an increased maximal heart rate and maximal double product. Bypass surgery does not affect the double or triple product at specific submaximal work loads. Of interest is the recent report by Bloch and associates[23] demonstrating an increase in exercise duration maximum rate pressure product and maximum heart rate in a group of patients after unsuccessful (all grafts occluded) myocardial revascularization, suggesting that increased myocardial blood supply is not the only mechanism by which bypass surgery improves exercise tolerance.

Long-term results of cardiac exercise programs

An improvement in cardiovascular fitness, an increased exercise capacity and a [illegible] creased anginal threshold would be sufficient motivation for many physicians to recommend exercise therapy for their patients. Other physicians and their patients, however want to know whether exercise therapy will decrease the incidence of myocardial infarction and prolong life. These remain unsettled questions at present. The multiple studies on rehabilitation of cardiac patients have recently been reviewed. Although several studies show a tendency to lower death rate and lower incidence of myocardial infarction, these studies suffer from methodological problems in terms of sample size and control groups. Kellerman[24] studied patients who participated in both short-term (4 months) and long term (12 to 42 months) exercise programs. Only those patients participating in the long term exercise program had a mortality rate different from control. These results imply that one must continue exercising for prolonged periods to have a beneficial effect in terms of reduced cardiovascular mortality rate. In two randomized control trials carried out in Scandinavia, no statistical improvement in the incidence of recurrent myocardial infarction or cardiovascular mortality could be documented.[25] These studies, however suffered from a high drop-out rate in the exercise group. No study has shown an increased incidence of myocardial infarction or cardiovascular mortality in patients who have been physically trained. A multicenter collaborative study might help to answer some of the unresolved questions.[11]

Exercise program

The prescription of an exercise program for patients with coronary artery disease must be individualized. The patient should undergo a medical screening procedure to assess the presence, severity and stability of anginal symptoms as well as to rule out signs of congestive heart failure, impaired cardiac output, valvular heart disease, severe hypertension, and other systemic disease. Certain drugs such as propranolol may impair the effectiveness of an exercise program by preventing the patient from achieving an appropriate heart rate.

Prior to prescription of an exercise program, a symptom limited exercise stress test is recommended to determine the individual's work capacity the possible occurrence of exercise-induced arrhythmias, and abnormal heart rate and blood pressure responses to exercise. The work load and heart rate at which the patient develops angina

cant ischemic ST depression should also be noted so as to keep his heart rate below this level during training.

The principles of an exercise program are the same in both normal patients and in those with coronary artery disease. The usual prescription calls for repetitive endurance type exercise with large muscle groups. Most work physiologists further specify the frequency duration, and intensity of exercise. A typical program would call for 20 to 40 minutes of exercise three to four times a week with an intensity of exercise of between 50 per cent and 80 per cent of the endurance capacity

Certain questions are left unresolved by present studies. The question of supervised vs. community based or home exercise has implications in terms of accessibility of a program to patients and allocation of health resources and cost. Some authorities recommend an indefinitely prolonged supervised exercise program for cardiac patients while others recommend an initial supervised program with graduation to unsupervised exercise after a specific period (3 months to 1 year) and periodic evaluation with exercise stress tests. Even in well-organized and supervised cardiac programs, the major cardiovascular complication rate (fatal and nonfatal) is approximately one in 26,700 man-hours of participation.[43] Another question which is unresolved at present is whether previously physically active post-myocardial infarction patients can resume previous athletic activity on a symptom limited basis without undergoing formal exercise testing and training. In spite of this common clinical practice, the safety of such activity has not been evaluated.

Conclusion

Exercise training is widely recommended as a tool to improve the cardiovascular function of selected patients with coronary artery disease. Following a period of physical training, the patient may perform specific activities (or tasks) at a slower heart rate and with a lower myocardial oxygen demand. The mechanism of this improved cardiovascular function is an increased efficiency of oxygen extraction and metabolism in the trained peripheral muscles. There is no evidence at the present time that exercise training alone increases collateral coronary circulation, nor does exercise training have either a direct beneficial or detrimental effect on the myocardium in man. Exercise training increases a patient's sense of well-being and may have a favorable influence on certain coronary risk factors.

The evidence that physical training programs have any effect on life expectancy or the incidence of coronary events is inconclusive. No study has demonstrated an increase in morbidity or mortality in cardiac patients participating in supervised exercise programs. Studies presently underway may help to answer this important question.

Many post myocardial infarction patients do not have the motivation, time, or money to enroll in a supervised exercise program. Facilities for such a program may not be available. For these patients the physician usually encourages a gradual return to full daily activities. In addition, many physicians encourage such activities as walking or other individualized, symptom limited but unsupervised exercise programs. Whether this type of program can substitute for a supervised exercise program and achieve similar physiological and psychological benefits is a question which has not been studied.

Exercise training programs, although based on sound physiological principles, should be subjected to the same cost–benefit analysis as other alternative forms of treatment.

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Annotations

The etiology of peripartum cardiac failure

Unexplained heart failure in the weeks after childbirth was first delineated in New Orleans; some 75 per cent of the patients were black, and it was common after twins and toxemia of pregnancy. Transient hypertension, arterial emboli, and recurrences after succeeding pregnancies were also noted. Doubts about the existence of a discrete syndrome were dispelled by Meadows, who found an incidence of 0.1 per cent of black deliveries in Chicago. Only in Korea has the incidence approached that in black American women. The few African reports culminated in a large series from Ibadan. More recently the syndrome has been found to be very common in Zaria, in northern Nigeria.

The acceptance of the syndrome has led to the tacit assumption of its unity. The incidence, however, varies from about 0.006 per cent of Caucasian deliveries to 1 per cent of Hausa deliveries in Zaria. Although the total number described annually from the United States remains roughly constant, the proportion of white patients has dropped from 24 to 32 per cent before 1966 to 11 per cent since. Further, edema was reported in only 56 per cent of Caucasian patients, and hypertension in only 31 per cent, whereas edema is almost universal in black patients, and hypertension occurs in over 75 per cent. Likewise, the gloomy prognosis in America, with a mortality rate of around 30 per cent within a few years, even after prolonged bed rest, contrasts with a mortality rate of only 11 per cent in Zaria, despite admission for only 15 days, continued breast feeding, and further pregnancies. Conclusions drawn from work on black patients may therefore not be universally applicable.

The etiology of the syndrome remains unknown. Glomerulonephritis, toxemia of pregnancy, beri-beri or other nutritional deficiencies, and an infective process were all suggested originally but have not been substantiated. Evidence of previous viral infection has occasionally been found, as have anti-heart antibodies, but myocardial pathology is nonspecific both macroscopically (hypertrophy, mural thrombi) and microscopically (necrosis, edema, lymphocytic infiltration, fibrosis). Acute hypertensive heart failure has been proposed, but the syndrome is normally one of congestive cardiac failure, and hypertension is relatively modest, and transient, and may be absent.

In Zaria, symptoms began before delivery in 18 per cent of patients, and we therefore retained the term "peripartum cardiac failure" (PPCF), even though only 2 per cent were admitted in pregnancy. PPCF was much commoner among the Hausa than in other groups, with a well-defined seasonal peak in July. It was associated geographically with the traditional Hausa puerperal customs of being heated twice daily on a baked mud bed over a fire, splashing themselves twice daily with scalding water, and eating large amounts of *kanwa*, dried lake-salt. Eighty-seven per cent of patients were hypertensive on admission, but this and cardiac failure both resolved dramatically on treatment with digoxin and diuretics. During follow-up, 22 per cent became hypertensive again after an average of 16 months, and recurrences of PPCF after further pregnancies were again highly seasonal, and closely associated with postpartum hypertension. Asymptomatic, transient postpartum hypertension (PPHT) was found in about 15 per cent of otherwise normal black American and Ibadan women for some weeks after delivery. In normal Hausa women attending a postpartum clinic, we found a pronounced seasonal variation in blood pressures of 140/90 mm. Hg or more, from 66 per cent in April to the seasonal peak in the onset of symptoms of PPCF to 31 per cent in November.

In considering the etiology of PPCF in Zaria, we noted the geographical links with postpartum heating and the consumption of 200 mmol. or more of extra sodium daily as *kanwa*, the seasonal and geographical links with PPHT, and the high incidence of hypertension in PPCF and recurrences of PPCF. We postulated that the *volume load* imposed by heating (customary and climatic) and splenomegaly and anemia, the *pressure load* imposed by PPHT and *kanwa*, and the *output load* imposed by heating and by infections combined to cause cardiac failure. Why this happens when pregnancy, especially pre-eclamptic or hypertensive pregnancy, has not led to cardiac failure remains a mystery. A puerperal liability to slippage of myocardial fibers is a speculative possibility.

Sanderson has recently pointed out from Zaria that cutaneous vasodilatation by heating may impair homeostasis of body-fluid volumes by lessening the rise in blood pressure caused normally by any increment in plasma volume. Excretion of a load would, under these circumstances, require a greater rise in cardiac output than usual, further stressing an ailing myocardium. (On the other hand, of course, the myocardium is at the same time spared from working against an increased pressure.) However, the normal regulatory mechanism is subject to independent alterations in renal blood flow even in left ventricular failure, and vascular reflexes are in fact maintained after brief acclimatization to heat. The postulated mechanism would not account for impaired cardiac performance during brief exposure to heat, since fluid would take time to accumulate. The principal load imposed by heating must be the increased cardiac output necessary to sustain increased dermal blood flow, with edema formation being secondary to increased capillary hydrostatic pressure, in turn due to increased arteriolar pressure (resulting from heating) and increased venous pressure (if the heart fails)—and exacerbated in the tropics by a decrease of plasma albumin in the "hungry season" before the harvest. Sanderson's hypothesis invokes at least a relative inability to raise the blood pressure in the puerperium as a cause of PPCF. Whatever the changes induced during the twice daily heating itself, we have shown in contrast significantly higher postpartum clinic blood pressures in nonedematous women during the seasonal peak of PPCF in May (146/92 mm. Hg) than when

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the incidence falls in October (128/78 mm. Hg).[14] Sanderson[16] also found a mean cardiac output of 6.3 L/minute in PPCF[19] in contrast to the low outputs found by others, which makes it difficult to explain the oliguria on admission and the rapid response to treatment; his full experimental and control data are awaited with interest.

The etiology of the syndrome elsewhere remains even more obscure. In global terms, PPCF and PPHT are both very common among the Hausa in Zaria, common in other black people, and rare elsewhere. PPCF is common in Korea, and hypertension likewise,[20] but PPHT has yet to be described. Korean and Japanese salt intakes are high, especially in the winter as salted vegetables, but are not further increased postpartum. Japanese blood pressures tend to be higher in winter[21] and it would be interesting to know whether there is a seasonal variation of PPCF in Korea, and if so whether the peak is in the hot summer months or in the winter when salt intakes (and blood pressures?) are higher. Experimental data on the ability of the normal kidney to escape from salt loading in the puerperium, and on the liability of the puerperal heart to dilatation when subjected to pressure load, might also promote further understanding of this intriguing syndrome.

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Hypertensive crises in spinal man

Before World War II, high spinal cord injuries were usually fatal within a short period after the accident. Because of the advances in acute and chronic management this is no longer true: there is an increasing population of spinal cord injured subjects in a stable form.

Most subjects with transverse lesions at T5 or above eventually have attacks of autonomic hyperreflexia. An stimulation of dermatomes and muscles supplied by nerves below the injury, especially manipulation of the perineum, genitalia, and distension of the bladder or rectum, evoke hypertension, bradycardia, headache, and in the face and upper trunk, sweating, flushing, and piloerection. The hypertension is often severe and prolonged, and may cause cerebral vascular accidents and death. Autonomic hyperreflexia has been mistakenly diagnosed as pheochromocytoma and toxemia of pregnancy and becomes a severe complication during surgical procedures involving traction of the viscera.

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The hypertensive crisis is the result of excessive stimulation of the preganglionic sympathetic neurones in the distal spinal cord stump,[4,5] and the striking bradycardia is probably due to excitation of the supra-spinally mediated baroreceptor reflexes.

This laboratory recently reported additional findings about this syndrome. During routine cystometry autonomic dysreflexia was induced in 11 quadriplegic subjects with transverse lesions between C6 to 8. Hemodynamic investigations in five of these subjects showed that at the end and height of the hypertensive episodes, which varied between 21 and 55 minutes, the average changes of mean arterial pressure, cardiac output, peripheral resistance and heart rate, compared with the control values, were +62 per cent, −1 per cent,† +61 per cent and −27 beats/minute, respectively. Thus, the large increase in arterial pressure, accompanied by parallel elevations of both sympathetic and parasympathetic nervous system activity was associated with no change in cardiac output and a highly significant increase in systemic arteriolar vasoconstriction.

Investigations were also done to determine if plasma volume decreased during the hypertensive crises, as occurs during intravenous infusions of noradrenalin. This would cause hemoconcentration of plasma proteins, including dopamine-β-hydroxylase (DβH), and alter interpretation of the latter increased activity as an index of sympathetic activity during the hyperreflexia. In eight of the quadriplegic subjects, at the end and height of the hypertensive episodes, the estimated average decrease in plasma volume was between 10 and 15 per cent. This hemoconcentration could have accounted for no more than one quarter of the rise of DβH activity measured in this and in previous study. Therefore, the increased DβH activity is a good indication of the rise in sympathetic activity during the syndrome.

The eight subjects were normovolemic in the control state, and the decrease in plasma volume of 10 to 15 per cent corresponded to a reduction of total blood volume of approximately 5 to 9 per cent. In normal subjects with intact compensatory sympathetic cardiovascular reflexes, such decreases in volume would cause no significant reduction of arterial pressure. If they had received drugs that would have reduced resting vascular tone and reflex sympathetic activity however that small degree of blood loss might have produced severe hypotension and syncope, even in the supine position. Despite the inability of the supra-spinally mediated baroreceptor reflexes (carotid sinus, aortic arch, and low pressure area receptors) to cause compensatory stimulation of the sympathetic neurones in the spinal cord below the transection, these symptoms did not occur in the quadriplegic subjects when the hypertensive state was quickly terminated by allowing the bladder to empty. These subjects appear to have essentially normal levels of adrenergic cardiovascular tone when not in autonomic hyperreflexia and to be able to compensate for minor blood volume disturbances through spinal reflexes[6] and the reduction of efferent vagal tone. It would, however be unwise to place them in seated or upright positions immediately after an attack because of the hydrostatic peripheral venous pooling. Additionally such "post attack" hypotensive complications might be considered a possibility if the patients' resting blood volume, vascular tone, or myocardium were depressed, which could occur in hot environments, during febrile states, and during administration of cardiovascular drugs. These pharmacologic agents will become more clinically relevant as the population of spinal cord injured subjects grows older and becomes prone to coronary heart disease and hypertension.

Headache is a characteristic symptom during autonomic hyperreflexia and can be very severe. Many have hypothesized that it results from passive dilatation of the cerebral vessels during the systemic hypertension. There is no correlation, however between its presence, absence, or degree of severity with the level of hypertension. [1-3] investigations in this area have not provided convincing results to support the hypothesis. As indicated previously the episodes of autonomic hyperreflexia are associated with simultaneous elevations of sympathetic and parasympathetic activity and prostaglandins are released during enhanced activity of both systems. In the present study the arterial concentrations of PGE_2 rose from an average control value of 0.34 to 0.57 ng./mL plasma during the crises. High doses of PGE_1 and PGE_2 in man typically produce flushing of the face and upper trunk and headache.[4,5] Intravenous infusion of PGE_1 at a rate of 5 to 20 µg/minute causes headache. Assuming a 90 per cent destruction during each pulmonary transit, these rates of PGE_1 infusion would produce arterial concentrations similar to those measured in this study at the time of the induced hypertension. It seems reasonable to hypothesize that the headache in this syndrome may be caused by the increased concentrations of prostaglandins. These symptoms could be the result of a direct biochemical effect or due to relaxation of vascular smooth muscles which would reduce the autoregulatory control of cerebral blood flow. In the latter instance, the headache might be due to a passive vasodilatation of the cerebral vessels during the hypertensive episodes.

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†p < 0.01
†not significant.

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The control of hypertension in the community no easy solution

Hypertension is an important public health problem. Health surveys have detected blood pressure elevation in approximately one in seven adult white North Americans, and in an even higher proportion of blacks. Hypertension in these persons constitutes a major risk factor in the development of serious cardiac, cerebral, and renal diseases. Currently available treatment for hypertension has been shown to reduce the likelihood of strokes. However it appears that most persons with hypertension are uncontrolled, either because they are unaware of their condition, aware but untreated, or treated inadequately.

In response to this problem, a number of community detection programs have been established to identify persons with high blood pressure and refer them for treatment. This report describes the Montreal hypertension screening project, which was undertaken with three specific aims: to assess hypertension control among adults living in the community, to learn why some persons with hypertension were not receiving treatment, and to determine if hypertension control differed among different groups reached by the program. People were screened in shopping centers (self-selected sample of 2,025 persons), workplaces (a self-selected sample of 8,306 persons) and homes (a random sample of 724 persons in four census tracts). The methodology has been described in detail elsewhere.

Of the shopping center and home samples, about 30 per cent were classified as hypertensive; half as many were so classified among those screened in their workplace, reflecting the fact that these persons were younger and perhaps healthier than those screened in shopping centers or at home. Another 10 per cent to 15 per cent of each sample were classified as borderline hypertensives and were referred to their physicians for re-examination.

Less than a third of persons with hypertension (Table I) had normal or borderline blood pressures recorded at the screening. Although many of the uncontrolled hypertensives were unaware of their disorder, substantial proportions treated were aware. Approximately one-quarter of all hypertensives detected in each setting were aware but untreated. About half of these individuals had received drug therapy previously. When the 254 persons who had discontinued therapy were asked why they had done so, 53 per cent indicated that they had done so on the advice of their physicians. Approximately one-seventh of all hypertensive subjects were uncontrolled despite therapy according to our classification.

The data from the household survey were analyzed by neighborhood. The populations in the various neighborhoods did not differ by age and sex. Two were working-class districts with mean household incomes of $7,000; one was almost entirely French-speaking and the other was mixed English and French-speaking. The other two districts were middle-income, with mean household incomes of $15,000; one was predominantly English and the other predominantly French. The prevalence of hypertension and the proportion of persons with newly discovered hypertension did not differ much among the four districts. In each district, large numbers of hypertensives were aware of their condition but untreated; in the middle-income districts these were mostly persons who had never received treatment, while in lower-income areas a substantial proportion had taken medication in the past but had discontinued it. The proportion of treated persons remaining hypertensive was similar in the different neighborhoods. The proportion of persons whose blood pressure was controlled to normal or borderline levels did not exceed 31 per cent in any neighborhood.

The data from home screening are presented according to household income in Table II. The prevalence of hypertension was inversely related to income. The proportion of persons whose hypertension was controlled did not differ among the three groups. Lack of awareness of their high blood pressure was least common in the group earning less than $7,000 per year. However, discontinuance of therapy was most common in this group, which included more women and persons over 55 years of age than the other two groups.

Discussion

In over two-thirds of those identified by us as hypertensive in each setting, the condition was uncontrolled according to

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Table I Control among persons categorized as having hypertension

Status	*Place screening conducted, % of subsample*		
	Shopping center (n = 930)	*Workplace (n = 1,197)*	*Home (n = 218)*
Controlled			
Normal blood pressure	16.8	12.0	7.8
Borderline hypertension	14.2	8.8	11.9
Uncontrolled	69.0	79.2	80.3
Unaware of condition	21.6	47.9	41.3
Aware of condition			
Never treated	12.7	14.0	12.9
No longer being treated	15.2	6.9	13.3
Receiving treatment but hypertension uncontrolled	18.6	9.8	11.9
History uncertain	0.9	0.6	0.9

our criteria. While determination of the presence or absence of hypertension at a single sitting is likely to result in overestimation of the incidence among those in whom the diagnosis has not been made previously, the likelihood is far less among those in whom the diagnosis has been made previously. While in a large minority of persons with uncontrolled hypertension the disease was newly diagnosed, we consider the most important finding of this study to be that an even larger proportion were either aware of their condition but remained untreated, were being treated inadequately, or were no longer taking antihypertensive medication. A striking and unexpected finding was that the majority of persons with previously treated hypertension reported that they had discontinued therapy on the advice of their physicians. This was particularly true among the people with annual incomes under $7,000. Lack of awareness was not peculiar to the low-income group.

Community control of hypertension must improve if we hope to improve the life expectancy of adults; the survival of men 50 years of age and older has hardly changed in more than 50 years. Several principal causes of death in this age group are diseases for which hypertension is a major risk factor. Efforts to improve control in populations have not been uniformly successful.[13-15]

Community programs for hypertension control are likely to be successful when they determine and take into consideration the relative numbers in their populations of persons with detected but untreated disease, persons in whom treatment has been discontinued by patient or physician, and persons in whom treatment has not been adequate to control their hypertension, as well as those with undiagnosed hypertension.

Are there special implications of this study for an American medical audience? Many of our data are consistent with other

Table II Hypertension control according to household income

Status	*Annual income; % of subsample*		
	< $7,000	$7,000-$15,000	> $15,000
Categorized as having hypertension at screening	27.7 (83 cases)	27.9 (73 cases)	22.8 (42 cases)
Status of control	*% of those with hypertension*		
Controlled			
Normal blood pressure	3.6	8.2	14.3
Borderline hypertension	13.3	12.3	4.8
Uncontrolled	83.1	79.5	80.9
Unaware of condition	28.9	50.7	47.3
Aware			
Never treated	9.6	13.7	16.7
No longer being treated	27.7	9.6	2.4
Receiving treatment but hypertension uncontrolled	16.9	5.5	14.3

studies conducted in the U.S., [illegible] but of particular interest is the finding that a substantial proportion of persons with previously treated hypertension reported that they had discontinued therapy largely on the advice of their physicians, that this was particularly true of persons with incomes of under $7,000, and that lack of awareness was not a particular problem of the low income group. In a country where access to medical care is more stratified by economic considerations than in Canada, low income patients are perhaps even more likely to be given poor advice by their physicians, or to be advised about the need for continued therapy in ways that they are unable to understand. Indeed, it would be surprising if the problem of compliance by both patients and physicians were not at least as great, and there is some evidence to suggest that this is the case; in one American study fully 24 per cent of dropouts from a hypertension clinic reported that they had stopped taking their medications on the advice of their physicians.

For those sectors of the population who lack access to competent practitioners with whom they can communicate and to whom they can relate, screening may do little more than transfer them from the category of "unaware" to another category of uncontrolled hypertension.

For those already aware of their hypertension, screening can be only part of the solution to the over-all problem. If in community reasons for lack of hypertension control are found to vary with such factors as socioeconomic status, it will be necessary, and should be possible, to design programs specific to the needs of particular groups.

In the United States, this will require improving access to effective care and affordable medications, as well as assuring

that practitioners are aware of, and are able to communicate to their patients the need to take antihypertensive medications continuously.

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Of the digoxin–diuretic cardiomyopathy

One of the most serious and extremely common types of cardiac disease at present is that produced by the injudicious use of digoxin and kaluretic diuretics. As indicated previously, it is not possible to digitalize a patient properly with the use of digoxin. This drug cannot produce a sustained smooth state of digitalization. When used according to the arbitrary dosages recommended by the PDR, intoxication is quite likely to follow. Furthermore the negative potassium balance produced by the kaluretic diuretics frequently used in conjunction with digoxin, and also used in arbitrary dosages, will increase the patient's sensitivity to digitalis and may even produce serious and often fatal cardiac arrhythmias. Since digoxin and kaluretic diuretics are usually used in patients with organic heart disease, the tendency for digitalis intoxication to develop is even greater and much more serious. The use of potassium supplements with these drugs may even complicate the problem further.

The digoxin-diuretic cardiomyopathy is [illegible] cardiomyopathy of serious nature and of great frequency. This disease of the heart needs attention. It is a highly fatal disease state, frequently mistreated and unrecognized, and is frequently made more complex by mismanagement. There is no excuse to intoxicate a patient with any preparation of digitalis. Digitalis must be used in the proper amount and dosage intervals to suit each individual patient, just as insulin is used, and not by arbitrary dosage rules or arbitrary routine orders. It is interesting that one of the most useful and important drugs in cardiology is the one most poorly prescribed today, and it is a common cause of cardiomyopathy—digoxin cardiomyopathy.

Physicians' Desk Reference. Published by Medical Economics Company, Oradell, N. J.

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to the Editor

ineral deficiency and atherosclerosis

the Editor

In the June, 1978, issue of the JOURNAL Drs. Chipperfield Chipperfield[1] published their interesting findings regarding differences in the mineral contents of normal and athero- heart muscle. I do not question the factual contents the paper, but would like to comment on the conclusions authors draw from them, namely that Western diet may deficient in some minerals and this deficiency may be in the prevalence of coronary disease. I do not agree this conclusion follows from the facts published in the article and, in any case, it is unlikely to be true.

Any mineral we need is probably also needed by other ly also by plants, and is likely to be obtainable from food. No animal species could survive if it had to rely on utrients which are not obtainable without undue difficulties its normal habitat.

In the course of evolutionary history no animal has ever lived on more varied and abundant diet than modern man in prosperous society. The whole world is combed for delicacies for his table, not even mentioning the vitamin supplement, calcium enrichment, iron tablets and whatever else is contained in food additives, drugs, medicines and the like. It is unlikely that there is any substance of which his intake is less than that of the inhabitants of the poorer countries of Asia and Africa. Yet it is he who suffers from atherosclerosis; the disease is virtually unknown in the poorer countries of the world. Another point to note is that atherosclerotic coronary disease was virtually unknown in Europe 300 years ago. Was the substance in question still abundant then and became scarce only in the recent past? This seems the main argument against the assumption that atherosclerosis can be deficiency disease.

There is, however one item of diet to which special consideration must be given, namely water. The fact that cardiovascular and cerebrovascular mortality rates are lower in hard water than in soft water areas could signify that hard water contains some substance of importance which soft water lacks. In the tropics, where atherosclerosis is virtually non-existent, large volume of water in extreme cases 10 liters in day can be lost by sweating and has to be replaced by drinking. If the hypothetical substance were obtainable solely from water, the intake of the inhabitants of tropical countries could be much more than ours. The supposition, however gives rise to number of difficult questions. Is there no water supply in Europe and North America with an exceptionally high content of this substance? Is there no water supply in Asia and Africa with particularly low content?

The apparent atherogenic properties of soft water have given food to great deal of thought and various possibilities have been suggested, including one by myself. Alternatives to the deficiency hypothesis rest on the fact that soft water is better solvent of some substances than hard water

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Reply

To the Editor

There seems to be more speculation than solid fact in Mr Seely's criticism of our paper.

The possibility of deficiency in mineral salts in the diet contributing to the development of ischemic heart disease has been suggested independently in dietary investigation published since our paper was submitted. Morris, Marr, and Clayton[1] found that normal men with a high calorie intake had lower incidence of ischemic heart disease than those with lower total calorie intake. This unexpected result might be accounted for if a low energy intake means that the diet is deficient in mineral salts or possibly vitamins. They also found that those subjects eating large quantities of brown bread had lower incidence of ischemic heart disease. We have calculated that the increased consumption of brown bread by their high-fiber group would provide 5 to 10 per cent of the magnesium needed to remain in balance, so the increased mineral salt content of brown bread as opposed to white bread might account for the benefit derived from the consumption of brown bread.

The possible importance of the mineral salt content of foods in the development of ischemic heart disease is discussed in more detail in a forthcoming article.

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Fatal hypotension in normal-dose nitroprusside therapy

To the Editor

W would like to report one death by hypotension that occurred two hours after an average-dose nitroprusside infusion was withdrawn.

A 42 year-old male, that weighed 60 kilograms and was

known to have scleroderma for two years, abruptly developed malignant hypertension, rapidly deteriorating renal function, and heart failure. On admission, in addition to extensive sclerodermatous involvement of the skin, physical examination disclosed a blood pressure of 210/130 mm. Hg, bilateral exudates and hemorrhages in the optic fundi, a third heart sound, moderate neck vein distension, and bibasilar crepitant râles. Serum creatinine was 6.3 mg./dl., hematocrit value was 28 per cent, and arterial blood gases showed: pH. 7.31, pCO_2, 32 mm. Hg, and total CO_2, 18 mmol./L. The electrocardiogram demonstrated left ventricular strain and there were early signs of pulmonary edema in the chest x-ray. Central venous pressure was 16 cm. H_2O. Aside from diuretics, the patient had not received any antihypertensive medication previously. In an attempt to lower blood pressure and to reduce cardiac afterload, a nitroprusside infusion was then begun, under constant electrocardiographic monitoring and with BP measurements at 3 minute intervals. The nitroprusside was given at an initial rate of 1 μg per kilogram per minute, which was subsequently increased to 3 μg/Kg./minute in order to maintain a BP of 160/95 mm. Hg. Ninety minutes after the infusion had been started and when the patient had received a total nitroprusside dose of approximately 13 mg., the BP fell to a systolic level of 80 mm. Hg and the nitroprusside administration was immediately stopped. Upon discontinuation of the drug, the BP failed to rise, and continued to drop slowly over the following 2 hours, not responding to leg elevation, the intravenous administration of norepinephrine or dopamine or a fluid challenge. Central venous pressure remained at 12 cm. H_2O and serum potassium was 5.3 mEq./L. Simultaneously the patient developed severe metabolic acidosis (pH = 7.10, pCO_2 = 21 mm. Hg, total CO_2 = 8 mmol./L.) that was treated with bicarbonate, and became progressively obtunded. Finally 125 minutes after discontinuation of nitroprusside, and when the BP had reached a systolic level of 30 mm. Hg, the patient sustained a cardiac arrest and could not be resuscitated. At autopsy there was no myocardial infarction, pericardial effusion, pulmonary embolus, central nervous system lesion, or internal hemorrhage that could explain the hypotension. Therefore, it seems logical to assume that nitroprusside was responsible for the progressive circulatory failure that ended in this patient's death. This is surprising, since it is generally accepted that when administration of the drug is stopped, the blood pressure rises to pretreatment levels within one to ten minutes.

Dangerous but transient episodes of hypotension have occurred when nitroprusside is used in combination with clonidine[1] or methyldopa. More significantly three fatalities associated with the use of nitroprusside for induction of hypotension during surgery have been reported.[4-6] All the fatal cases had received large total doses of nitroprusside (from 400 to 750 mg.) in short periods of time and developed progressive hypotension and metabolic acidosis after discontinuation of the drug. Cyanide is the immediate byproduct of nitroprusside metabolism and it has been suggested that cyanide toxicity caused the death of all these patients. A check of blood cyanide levels alone cannot be expected to detect evidence of significant cyanide poisoning, since much of the freed cyanide can bind quickly to tissue cytochrome oxidase. Cyanide toxicity should not be confused with thiocyanate excess, which is an entirely different problem.

Our patient, as well as all the human fatalities previously reported, developed progressive hypotension and metabolic acidosis despite discontinuation of the nitroprusside infusion. This strongly suggests a common underlying cause, namely cyanide toxicity. However the case herein reported differs from the previous ones in that: (1) renal insufficiency was present, (2) the patient had neither received any antihypertensive drug other than nitroprusside nor was he anesthetized, and (3) the total dose of nitroprusside received was 30 to 60 times lower.

We suggest that irreversible hypotension probably caused by cyanide toxicity can occur even after small doses of nitroprusside, and therefore the drug must be used with great caution. Considering that hydroxocobalamin has been shown recently to prevent cyanide toxicity from large doses of nitroprusside, it would appear appropriate to administer this drug prophylactically to all patients receiving nitroprusside, even in small dosages.

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CPR and seizure

To the Editor:

The cardiopulmonary resuscitation (CPR) manual for Basic Cardiac Life Support for instructors[1] is certainly most complete and impressive. The 132 pages, appendix, and text are thorough, readable, and basic. It seems to me, however, that there is a gap in the manual leaving "uncovered" a common resuscitative event, namely the occurrence of seizure activity with syncope.

During major motor seizure due to a primary focus or hypoxic in origin, finding pulses may be difficult if not impossible, apnea is standard, and breathing for a patient is impossible. These problems and others are great enough for medically trained personnel, but what about the number of

-medical CPR trainees? Are they to be trained in seizure what to do if it occurs, how and when to start PR? Obviously these are not the only implications and

No mention is made in the manual of what to do in the face of convulsion. T ignore this problem is to leave large of CPR "graduates unprepared for a common and troublesome situation.

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Data analysis in BP measurement

T the Editor

Dr. L. A. Geddes and S. J. Whistler are to be commended for their efforts to provide guidelines regarding the probable error in blood pressure measurements when using cuffs of the wrong width. Unfortunately it seems that the statistical method (linear regression) used to determine these errors has been employed incorrectly It is my understanding that the data points in linear regression or correlational analyses must represent independent samples. Thus, performing linear regression on an array of data points where each subject has contributed two or more points to the array violates one of the assumptions underlying this statistic.

Since repeated measurements on the same subject are correlated to some degree, it is apparent that this methodology can bias the results of linear regression. This practice of using linear regression and correlation statistics when repeated measures designs have been employed seems widespread in the literature. For example, there are several papers[2] concerning the correlation between direct and indirect measurements of blood pressure where the same statistical error has been made.

In light of the above remarks, I hope that qualified biostatistician will be invited to comment on this problem in the near future. Hopefully the statistician's comments will also include suggestions of other means to analyze these types of data.

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Reply

T the Editor

I appreciate the opportunity to respond to Dr. Schaefer letter regarding our paper, "The error in indirect blood pressure measurement with the incorrect size of cuff, which appeared in AM. HEART J 96:4, 1978.

As suggested by Dr Schaefer we have consulted statisticians who do not disagree with the method that was used to present our message. They did point out certain techniques that could hav been used in acquiring the data. For example, it would have been ideal to have an array of cuffs of different size so that the mismatch would hav been the same above and below the recommended cuff width for highest accuracy Unfortunately only restricted range of cuffs is available; therefore, the study had to be conducted with them.

Perhaps it would be desirable to restate our message, which is to make the point that the indirect measurement of blood pressure can be high or low if cuff is too narrow or too wide. The protocol presented allows anyone to repeat the procedure and prove our point. W do not state that the optimum cuff width is 40 per cent of the arm circumference; we merely used this alue which has been recommended and used for years.

The only underlying assumption was that the subjects blood pressure remained constant when measured with the three cuffs. Although the study would have been better if direct pressure had been compared with indirect pressure, unfortunately the resources for such study were not available to us. No statistical inferences were made from the linear regression line which was merely used to illustrate the nature of the mismatch.

Regarding the rat blood pressure studies, we cannot comment, since the optimum cuff size for the rat tail is not known.

W thank Dr Schaefer for his compliment on our efforts to provide guidelines regarding the probable error in blood pressure measurement.

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The benefits of coronary artery bypass surgery A suggestion for objective evaluation

To the Editor

The controversy over the benefits of coronary artery bypass surgery continues. Like huge conflagration it occasionally

quiets down a bit only to flare up again either in scientific meetings or on the pages of a medical periodical. The recent VA study for example, has had the effect of gasoline thrown upon the flames, generating rebuttals and defenses of the series. Apparently retrospective, prospective, and even many highly enthusiastic anecdotal studies have failed to solve the controversy nor do I think they will, for one group's careful study is another's poorly selected series.

Margaret Albrink[3] once stated (discussing another controversy this one over the treatment of diabetes mellitus), "Where there is controversy there is insufficient information with which to resolve the controversy This I feel will continue to be the situation with coronary artery surgery unless one emerges with enough courage, perseverance, and patience to resolve these disagreements once and for all.

Many of us remember the short life of the internal mammary artery ligation operation. Specifically one surgeon decided that by ligating both internal mammary arteries additional blood flow could be diverted to the coronary artery systems and thus relieve the ra ages of coronary artery disease. I had a patient who underwent this procedure because of severe angina. The operation was, in a small way quite successful for the patient, young man of 36 years, who had no further angina postoperatively Unfortunately he died suddenly two years after surgery This particular operation might still be performed today had it not been for the excellent work of E. Gray Dimond[4] and his associates. They assembled a series of patients half of whom had the actual ligation of the artery performed and the other half of whom underwent sham operation. This latter procedure consisted merely of making the same skin incisions as were done for the ligation procedure, but going no further There was, upon follow-up, no greater or lesser relief of symptoms in the ligated group than in those who had the controlled procedure. This experiment forever interred the internal mammary ligation procedure.

The one benefit of the coronary artery bypass surgery that seems reasonably agreed upon is that angina pectoris, at least for while, is relieved by this procedure. Using only angina as an end point, I suggest that an experiment similar to Dimond' be performed t one or more acti and prestigious cardiac centers. More specifically group of anginal patients would be assembled and divided into two carefully matched groups. The first would be subjected to the full coronary bypass procedure The second group would have exactly the same operation with the same incisions up to the point where the e is removed and the graft is performed. The incisions, of course, ould include those in the femoral area, and leg, as w ll as in the chest. However the vein would not be disturbed. The incision would also include the sternal splitting and thoracotomy attendant on the procedure Neither group would know which operation they had received. The names of each group's members would be carefully shielded and limit of two years would be set for evaluation.

Of course, certain precautions, in addition to full disclosure, would have to be taken. It would be quite desirable to ha this series and all expenses related to it funded, particularly by governmental gency The Government should certainly be eager to do this, since this operation is expensi and annually adds millions to medical care costs Naturall the entire procedure would be free to participants Surgeons and physicians working on the project should be guaranteed malpractice protection. Finally should the sham operation produce less benefit than the actual one, members of this group cou have a second operation performed at no charge. Lastly, stipends should be paid to the volunteers.

Under these circumstances, could such a group be asse bled? One would think so. There are always people who cra something a bit different from their usual existence. There a others who are anxious to aid in the relief of suffering and help humanity regardless of their motivation. There will b cardiac patients anxious to learn the truth just for the pea of mind that truth often brings.

If such a group can be assembled, will it be possible t gather the surgeons and cardiologist necessary to do th experiment? Again, one would hope so. Surgeons, I think, te to shy away from experiments of this nature. They have great need to believe that their efforts and excellent techniq will lead to the desired results. This attitude has been one the obstacles in eliminating radical mastectomy from th surgical armamentarium. The surgeons fear unnecessar procedures because the unexpected may occur. Double-bl experiments are done with drugs, hich also have the dangers, and surgeons should not flinch from such related studies. One should remember that the search for truth of excellence is one of the great goals of medicine.

The fame and prestige accruing to these participants woul be quite great. They would indeed be performing a gre service to cardiac patients everywhere, and they wou strengthen the practice of careful experimentation.

Finally one may ask what interest do I, a nonacademic cl rural physician, have in such a study Firstly I am a cardi ogist, anxious like all of us to help my patients to the great Also, I am quite tired of reading all the articles and learned all the ayes and nays" concerning this procedure. Th charts, graphs, and tables get more numerous, duller, a more tortuous in each issue of the heart journals. Also, at a older age, I am a bit of a skeptic. Too many wonderful thi hav appeared over the years on the medical scene only t vanish under the warming sun of knowledge, like morning fo in a country hollow

Unfortunately this is a late time to make such a propos The attraction of talented doctors to this procedure has be spectacular It has become one of the greatest surgical extr aganzas of our time.

Suggesting objective evaluation t this period seems alm akin to asking handful of volunteers to stem a tremendo army Still, the word "placebo lingers in the minds of som based in part on past surgical methods for the relief of angina The in estigation suggested in this paper seems necessary t prove or disprove the efficacy of this latest of surgical metho to benefit coronary artery disease. Hopefully it will b done.

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Clinical use of spironolactone

To the Editor

I would like to make the following comments concerning the clinical use of spironolactone in the review article by Ochs and associates in your September, 1978, issue. (Am. Heart J. 96:389, 1978).

The authors state that spironolactone is an effecti diuretic agent in patients with edema or ascites from heart failure, cirrhosis, or renal impairment and does not directly influence renal blood flow or glomerular filtration rate.

I would like to disagree that spironolactone could be used in renal impairment. This is especially true when renal impairment is associated with oliguria. In patients with renal impairment, potassium blocking diuretics could induce dangerous levels of hyperkalemia, at times even requiring dialysis. Fernfield and colleagues[1] describe case of fatal hyperkalemia in the absence of renal impairment.

Also, since insulin plays crucial role in potassium homeostasis, the use of spironolactone will ha to be implemented with caution in diabetic patients, with or without renal impairment.

Ammon and co-workers[2] hav described diabetic patient who developed hyperkalemia after hypertonic glucose infusions, despite normal plasma and urine aldosterone levels.

Goldfarb and associates[3] also describe two insulin-requiring diabetic patients with hyporeninemic hypoaldosteronism associated with hyperkalemia in whom the high serum potassium was raised further by glucose.

I would like to conclude by saying that spironolactone could result in dangerous hyperkalemia in patients with renal impairment. Also because insulin play crucial role in potassium homeostasis, diabetic patients, with or without renal impairment, are also prone to develop hyperkalemia. This drug could be used with extreme caution in patients with renal impairment if serum potassium could be monitored frequently.

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Reply

To the Editor

Dr Vaz has re-emphasized potential hazard of spironolactone therapy clearly stated in our paper as follows: Hyperkalemia clearly is the most important and serious potential complication of spironolactone therapy The risk is greater in patients with renal insufficiency and those who receiv potassium supplements. Data from the Boston Collaborative Drug Surveillance Program document this problem in detail. Thus administration of spironolactone to patients with renal insufficiency requires caution and careful consideration of the risks. The possible susceptibility of insulin-dependent diabetic patients to disorders of potassium homeostasis, spironolactone-induced or otherwise, requires further study

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Effects of glucagon

To the Editor

I was interested to read the article "Cardiac dose response relationship for intravenously infused glucagon in normal intact dogs and man, by Smitherman, Osborn, and Atkins, which appeared in the September 1978, issue of Am. Heart J (96:383, 1978).

Glucagon has been shown to be an effective inotropic and chronotropic agent in the treatment of shock but not congesti heart failure.[1-4] Kones and Phillips, however noted that the condition of patients with acute heart failure was improved while the condition of those with chronic heart failure and associated pulmonary hypertension was made worse. Glucagon does not produce excessive tachycardia and may even protect against digitalis-induced arrhythmia. More important is its ability to potentiate other inotropic agents.

Recently glucagon has been found to significantly decrease the pulmonary vascular resistance. Demling and co-workers[6] determined that the principal site of action may be on the arterial side of the capillary Patients with disease such as hypoxia-induced or primary pulmonary hypertension, where arterial resistance is increased, may benefit by glucagon.

Hemorrhagic or septic shock increased venous resistance and glucagon would be less beneficial.

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Book reviews

Coronary Heart Disease, Exercise Testing and Cardiac Rehabilitation. Edited by William E. James, Ph.D. and Ezra A. Amsterdam, M.D., New York, 1977 Stratton Intercontinental Medical Book Corporation, 336 pages. Price $27.50.

These proceedings of an international congress on coronary heart disease, exercise testing, and cardiac rehabilitation provide readers with opinions and practices around the world on an important subject. The book contains 25 papers about equally divided on epidemiology and management, exercise testing, cardiac rehabilitation, and workshop summaries. This reviewer found nothing really new among the papers nor any convincing data to support the cardiac benefits of exercise so frequently discussed in the medical and lay literature. For example, the risk factors for coronary heart disease (infarction and sudden death) are listed in Table I, page 25. But, is smoking itself risk factor or are factors associated with smoking the true factors? On page 30 the use of aspirin and lipid-lowering drugs (nicotinic acid, clofibrate, and cholestyr amine) are recommended in the therapy of coronary atherosclerosis. But, are they effective or just contemporary fad? These and other aspects of coronary heart disease are discussed, but the reader unless he is critical in his evaluation, will be convinced that certain therapeutic procedures are effective. This applies for exercise as well. The book does clearly present the present attitudes and concepts on coronary heart disease, however. The text is well written. Coronary heart disease remains an extremely important health problem and this book describes the approaches to the major problem throughout the world. The critical reader and those who follow the medical literature will find little new in this publication. Those physicians who do not follow the medical literature closely will find the book to be good single volume on subjects frequently discussed in the management of ischemic heart disease.

Boston Colloquium on Cardiac Pacing. Edited by J. Warren Harthorne and Hilbert J. Th. Thalen, The Hague, The Netherlands, 1977 Martinus Nijhoff BV Publishers, 185 pages. Price $18.50.

This small book is very good concise discussion of an important advancement in cardiology. The presentation is done with good taste and planning. Although it is of only few pages, it is complete and thorough and directed for the practicing general physician, cardiologist, and cardiac surgeon. History technic, instrumentation, indications, methodology and follow-up of patients are among the subjects presented. As in all symposia, the question and answer section at the end of the book is quite interesting. This is very good concise book on cardiac pacing. Dr Paul Zoll is properly and nicely recognized as the originator of the pacing concept and management of cardiac arrest and complete heart block. Readers will learn great deal from this book.

Cardiomyopathy and Myocardial Biopsy. Edited by M. Kaltenbach, F Loogen, and E. G. J Olsen, Berlin, Heidelberg, New York, 1978, Springer Verlag, 337 pages.

This book written by many contributors is concerned primarily with light and electron microscopic pathology of the myocardium of patients with cardiomyopathy. It is evident from the discussions that there are no characteristic morphologic changes of the different etiologic types of cardiomyopathy. The pathologic changes, including ultrastructural ones, are well known to those who are interested in the cardiomyopathies, but this book is good summary of the morphologic changes for those who are not directly engaged in cardiac pathology. The classification of the cardiomyopathies outlined on page XV is brief. There is no consideration given to the cardiomyopathy of the aging process (senile cardiomyopathy or "presbycardia") or ischemic cardiomyopathy. The latter is the most common etiologic type. The book is well written, the contributions selected are important, and the illustrations are good. The clinical value of myocardial biopsy is not critically justified. In short, is the risk and expense of myocardial biopsy necessary helpful, and sufficiently representative for clinical evaluation of the cardiac state when an expert cardiologist is available for evaluation of the patient without cardiac muscle biopsy? This reviewer thinks not.

Brain and Heart Infarct. Edited by K. J. Zulch, W Kaufmann, K. A. Hossmann, and V Hossmann, Berlin, Heidelberg, New York, 1977 Springer Verlag, 349 pages.

This symposium is concerned with cerebral circulation and with myocardial circulation. The papers are not concerned with the influence of one upon the other, such as the effects of impaired cerebral blood flow on the myocardial blood flow. The many short papers discuss hypertension and cerebral blood flow hypotension as risk factor, coronary arteriosclerosis and ischemic heart disease, the heart in hypertension, risk factors, cerebral arteriosclerosis, cerebral ischemia, etc. These brief papers are interesting and source of interesting review of the problems of impaired cerebral and myocardial circulations. The contributors are from all over the world. This is an interesting book on two important problems in medicine, cerebral circulation and myocardial circulation.

Books received

Isozymes: Current Topics in Biological and Medical Research, vol. I. Edited by Mario C. Rattazzi, John G. Scandalios, and Gregory S. Whitt, New York, 1978, Alan R. Liss, Inc., 202 pages. Price $16.00.

Isozymes: Current Topics in Biological and Medical Research, vol. II. Edited by Mario C. Rattazzi, John G. Scandalios, and Gregory S. Whitt, New York, 1978, Alan R. Liss, Inc., 1 6 pages. Price $14.00.

Evaluations of Drug Interactions. Second ed., Supplement. Washington, D. C., 1978, American Pharmaceutical Association, 521-626 pages.

Medical Physics. By John R. Cameron and James G. Skofronick, Somerset, N J 1978, John Wiley & Sons, Inc., 615 pages. Price $21.95.

E. A. Stead What this Patient Needs is Doctor Edited by Galen S. Wagner, Bess Cebe, and Marvin P Rozear, Durham, N. Carolina, 1978, Carolina Academic Press, 344 pages. Price $9.75.

Operative Surgery 3rd edition. By Charles Rob and Sir Rodney Smith, Sevenoaks, Kent, England, 1976-1978, Butterworth & Co., Ltd., 493 pages. Price $99.95.

Announcements

Woods Hole residential laboratory courses

The Marine Biological Laboratory Woods Hole, Massachusetts, will conduct a series of residential laboratory courses on topics related to electron microscopy A brief list of these courses is:

April 16 through 21, 1979. Freeze-etching in electron microscopy Instructor-in-Chief, Russell Steere, USDA, Beltsville.

April 22 through 27 1979. Biological electron microscopy for technicians. Instructor Morton Maser Marine Biological Laboratory

April 29 through May 4, 1979. Scanning electron microscopy in the biological sciences. Instructor Bruce Wetzel, NIH.

May 6 through 11, 1979. Electron microscopy in clinical diagnosis. Instructor Harry Carter St. Barnabas Hospital, Livingston, N J

May 13 through 25, 1979 Electron microscopy in the biological sciences. Instructors, Blair Bowers, NIH, and Morton Maser, Marine Biological Laboratory

Application materials and additional information on all courses may be obtained from Admissions Office, Marine Biological Laboratory Woods Hole, Massachusetts 02543. Telephone (617) 548-3705.

Education for the cardiac patient

A two-day seminar entitled Education for the cardiac patient, will be presented in Hershey Pennsylvania, on April 19 and 20, 1979. Sponsored by the American Heart Association, South Central Pennsylvania Chapter the seminar is directed to registered nurses and allied health professionals. For further information, contact Program Director 3805 Paxton St., Harrisburg, Pa. 17111 Telephone (717) 564-7748

Physicians Workshop in Electrocardiography

A Workshop in Electrocardiograph for physicians nd interested medical personnel will be offered on May 3 through 7 1979, t the Caribe Hilton Hotel, San Juan, Puerto R[illegible] The workshop will be sponsored by the Rogers Heart Fou[illegible]tion. For further information, contact. Anne S. Cros, [illegible]tive Coordinator Rogers Heart Foundation, St. Anth[illegible] Hospital, St. Petersburg, Fla. 33705. Telephone (813) [illegible] 0790.

Health hazard appraisal. clinical information consumers and practitioners

A two-day symposium on health hazard appraisal [illegible] presented on Saturday and Sunday April 21 and 22, 19[illegible] the Sheraton-Palace Hotel, San Francisco. Primary [illegible] physicians, nurses, pharmacists, health educators and [illegible] agencies concerned with the prevention of disease and [illegible] promotion of health will be interested in the program. [illegible] deal with the major causes of mortality current epidemi[illegible] risk factors, their pplication to risk estimation for [illegible] individual, and their pplication to preventive [illegible] programs. CME credit is vailable.

For more information regarding this symposium, call [illegible] 666-2894.

Pediatric Echocardiography symposium

The Department of Pediatric Cardiology University H[illegible]tal, Lund, Sweden, will sponsor symposium on Ped[illegible] Echocardiography on June 6 through 9, 1979. The subje[illegible] be covered will include: two-dimensional echocardiogr[illegible] pulsed Doppler echocardiography the contrast-echo m[illegible] echocardiographic studies of left entricular function, echocardiographic diagnosis of complex heart malforma[illegible] such as transposition of the great arteries and the univ[illegible] ular heart. The symposium leaders will be several sp[illegible] from Europe and the United States. For further inform[illegible] contact. M. Håkanson, The Secretariat, Department of [illegible]atrics, University Hospital, S-221 85 Lund, Sweden.

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Editorial

The cost and benefits of segregation (by age)

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A document drafted by the Section of Pediatric Cardiology (American Academy of Pediatrics) inadvertently calls attention to an anachronism, the free-standing pediatric hospital, and the segregation it represents. Since recommendations made in this document may affect all cardiologists and cardiac surgeons, the implications should be of interest to the readers of the AMERICAN HEART JOURNAL.

The standards are presented "for use by health planning agencies and health service organizations to evaluate existing pediatric cardiac centers and to establish the need for the development of new centers." Subsequently it becomes clear that the envisioned application of these standards is to prevent the development of new centers and to encourage the consolidation of existing ones, based on "the principal objective of medical care to reduce costs." They assert that cost-effectiveness will be improved by consolidation. However, their attention to cost-effectiveness is subsequently diverted by an obvious bias for pediatric hospitals. In the introduction, the Section states that they are "in concert with previous standards," and cite an Inter-Society Commission report. That report reasonably approaches cost-effectiveness from a five-day operating schedule, at 80 per cent capacity, and arrives at a minimum number of four open heart procedures weekly or 200 procedures annually. The Section of Pediatric Cardiology, however, asserts that 100 procedures would be adequate in a pediatric hospital, without explaining how a 40 per cent utilization would be efficient. In fact, underutilization leads to excessive unit costs in most pediatric hospitals, outside of a handfull of giant cities.

The reasonableness of free-standing pediatric hospitals should be examined very carefully at this time. This problem was reviewed in a thoughtful and convincing article by Haggerty ten years ago[1]: his community and medical school decided against "segregating all child care in a children's hospital, with its inevitable isolation from obstetrics, medicine and the basic sciences." The intellectual isolation, although deadly over a long period, is not as unfortunate as the physical isolation from obstetrical facilities of general hospitals. Good obstetrical and pediatric practice now mandate that transport of the premature infant is best accomplished *in utero* and delivery should be arranged in a hospital equipped and staffed for neonatal intensive care. Needless to say, pediatric hospitals do not accept maternity patients, and consequently the most exciting and rapidly growing branch of pediatrics is split off from the rest of pediatrics in communities that segregate the remainder of infants and children into free-standing hospitals.

What about the other end of the pediatric spectrum? How many 20-year-olds can you think of who would like to be hospitalized on a "children's ward"? How many pediatricians are really prepared to prescribe contraceptives and diagnose

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venereal disease or drug addiction? (The Section claims "birth to 21 years old" as their rightful patient population)

The social need for pediatric hospitals once existed, when hospitalization for rheumatic fever osteomyelitis, and tuberculosis required months or years. The milieu for those youngsters was crucial. With modern therapy most children are in and out of a hospital in a remarkably short time and the greatest kindness to the child, in Osler s words, lies in the correct diagnosis (and treatment) Kindness and lovely murals are not a substitute for excellent, cost-effective care for children.

A suspicion grows in my mind that pediatric hospitals have survived because they are a comfortable ghetto for pediatricians. (Pediatric hospitals are also a wonderful ego-trip for the wealthy lay volunteer) Although a ghetto may reduce the number of daily insults for the inhabitants, their long term well-being, as well as that of the larger community depends on integration. Similarly integration within the mainstream of medical practice is essential for the long term health of pediatrics, *and* children.

Integration of pediatric care is particularly important for cardiovascular training. At present, relatively few trainees in adult cardiology ever see a child with congenital heart disease consequently they rarely see congenital heart disease. Yet, most graduates will practice in small or moderate sized communities where there are no pediatr cardiologists, and the internist cardiologist will b consulted about the occasional child with a murmur A major part of the blame for th situation is the segregation of children, both by hospitals and by training programs in pediatr cardiology Although there will always be a ne for pediatric cardiologists in a few major centers, it is reasonably clear that fewer pediatric cardi ologists need to be trained, and that more subspe cialty experience in children should be added t the training of adult cardiologists, preferabl supervised by a pediatric cardiologist.

The costs of segregation by age are substant. and the benefits, small. The current push laymen to improve care and reduce costs sho not be subverted by accepting inefficiencies free-standing pediatric hospitals. The cardiov cular community should involve itself, and passively accept self serving "standards th perpetuate segregation of children with he disease.

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Clinical communications

Modification of Type A behavior in infarction patients

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Role of Type A behavior pattern in pathogenesis of ischemic heart disease

Approximately 18 years have elapsed since we first presented the concept that a particular Type of behavior pattern (Type A)† might play a part in the pathogenesis of clinical ischemic heart disease. Since that time we have completed many additional clinical, epidemiological, and laboratory studies concerning this possible relationship. The results of most of these studies have been described in recent reviews.[3-4] Also a number of other investigators[illegible] have conducted a variety of clinical and epidemiological studies that had been designed to determine if the components making up Type A behavior pattern may be involved in the causation of ischemic heart disease. Almost without exception, as Jenkins[14] recently has pointed out, these studies have suggested that such involvement exists.

Although there has been this widespread affirmation of an apparent associational relationship between Type A behavior and the prevalence as well as the incidence of ischemic heart disease, there have been few or no studies either confirming or denying the second concept that we also had presented, namely that Type A behavior also appears capable of inducing several phenomena that are contemporaneously considered as risk factors for ischemic heart disease.

Thus few of our colleagues appear to have taken note of our studies suggesting that Type A behavior may not only elevate the plasma cholesterol,[illegible] triglyceride,[illegible] norepinephrine,[illegible] corticotropin,[illegible] and the insulinogenic response to glucose, but may also enhance the clotting of blood [illegible] and the sludging of erythrocytes.[illegible] Nor have they paid too much attention to our data suggesting that heavy cigarette smoking and the prevalence of hypertension are predominantly found in Type A subjects.

This failure to recognize the possible primacy of Type A behavior in the development of these various abnormalities (most of which are presently recognized as "coronary risk factors") conceivably may be creating an almost absurd clinical state of affairs in which attempts are being made to prevent initial or recurrent ischemic heart disease by ignoring its chief cause and concentrating solely on abolishing the secondary biophysical and biochemical abnormalities or the noxious habit patterns (e.g., cigarette smoking, physical indolence) possibly generated by this same overlooked cause. Also a failure to recognize that this same overlooked causal factor possibly may exert its pathogenetic effects via *multiple* biochemical pathways could lead to a second rather irrational clinical state of affairs in which only the least important biochemical deviation may receive therapeutic attention.

Such focused attention upon a single biochem

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†A complete definition of Type A behavior pattern can be found in both references 3 and 4. Suffice it to state here that the pattern is an action-emotion complex exhibited by individuals who are engaged in chronic incessant endeavor to accomplish more and more in less and less time (i.e., a sense of time urgency or "hurry sickness") and who also usually (but not always) exhibit a "free-floating" but frequently elaborately rationalized hostility. This hostility is described as "free-floating" because it so readily vents itself on the slightest of various provocations. A subject is believed to possess severe Type A behavior pattern when he exhibits both of the above components in extreme degree.

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ical aberration (to the exclusion of other even more important abnormalities) is particularly apt to occur if the deviation can be easily measured. For example Type A behavior can cause both chronic excess production of norepinephrine[14] and also chronic elevation of plasma cholesterol.[1-] But only the latter substance until very recently has been readily measurable. This may be one of the reasons why so many thousands of studies concerning the possible role of cholesterol and only a mere handful of studies concerning that of norepinephrine in the pathogenesis of ischemic heart disease have been done. The total prophylactic inefficacy attendant upon the chemical lowering of the plasma cholesterol that was observed in the National Coronary Drug Project[20] should serve notice that such focalization of our efforts could prove to be disastrously misdirected.

II Contemporary difficulties in modification of Type A behavior in persons still free of clinical ischemic heart disease

A physician, even if he is eager to attempt to modify Type A behavior pattern in those of his patients who exhibit this pattern, still cannot hope to *achieve any significant success unless these patients already have suffered a myocardial infarct* Why is this so? Because of the following reasons

First and most important, the possession of this behavior pattern not only is a source of pride to most of those persons afflicted with it but its possession also imparts to them some sense of security Strangely they almost invariably attribute to this behavior pattern the credit for any socioeconomic or professional success they presently possess. As a consequence, they fear and will resist any regimen that aims to modify either their sense of time urgency or their free-floating hostility the two components of the Type A behavior pattern.

Second, it is very difficult for the Type A subject, who is quite pragmatic to comprehend how an abstract entity Type A behavior can lead to an actual arterial lesion. Yet Type A subjects appear quite ready to accept dietary intake of excess cholesterol, smoking, and hypertension as precursors of coronary artery disease, although even we physicians aren t sure as yet how these "risk factors" actually produce ischemic heart disease.

Third, even if subjects with severe Type A behavior can be convinced that this type of behavior may bring on the early onset of clinical ischemic heart disease, they almost invariably believe that it will be the other fellows with Type A behavior not themselves, who will suffer prematurely from an infarction.

Fourth, at this time the very few cardiologists who do attempt to modify Type A behavior not only encounter resistance and hostility from the Type A patients, but also sometimes from some of their fellow cardiologists. Indeed, as Blankenhorn and colleagues[3] recently have pointed out in a Letter to the Editor of the *Annals of Internal Medicine* the majority of cardiologists do not have adequate patience to alter or eradicate the other coronary "risk factors (i.e., the dietary smoking, and exercise habits) of their coronary patients. What degree of sufferance would these same cardiologists exhibit to a therapeutic regimen that would include behavior alteration which requires many hours not only of the patients' time but also their own? Yet alteration of Type A behavior requires from the cardiologist precisely such expenditures of time.

Finally it is not easy to maintain a regimen indefinitely that never provides positive or *unequivocal proof* of its possible prophylactic effectiveness. This is particularly the case in the treatment of impatient Type A subjects.

III The modification of Type A behavior in post-infarction patients

A. The reasons why behavior modification can be accomplished in most post-infarction patients. In view of the above-described assumption

*The majority of Type A subjects make no secret of the fact that they believe that it has been the Type A subjects who have made the United States the great nation that [illegible] They also frequently express contempt for Type B persons [illegible] great numbers of political, industrial, and professional leaders who exhibited Type B behavior are pointed out to these Type A subjects the information appears to fall on quite deaf ears

†Drs. Blankenhorn and associates in their Letter to the Editor of *Annals of Internal Medicine* propose that the patients [illegible] alter their high risk dietary and smoking indiscretions be shielded from their Type A cardiologists by interposing trained paramedical personnel who would actually meet and treat the patients. I do not think that their proposal will solve the problem because, from my experience, Type A cardiologists can be expected to accept and trust only paramedical personnel who also exhibit Type A behavior.

insurmountable difficulties in modifying the Type A behavior of *apparently healthy subjects*, some cardiologists[1] believe that it is similarly impossible to modify Type A behavior when it is encountered in patients who already have suffered a myocardial infarct. Such cardiologists, however, are wrong in this belief. But unfortunately most of them probably will continue to so believe because they will not take the time and also acquire the requisite expertise to make even an attempt to alter the Type A behavior in their post-infarction patients.

Why can Type A behavior be modified in the post infarction patient when it appears so difficult to achieve this in the healthy subject? There are several reasons. First, many of these patients during their convalescence from their infarction for the first time in perhaps many years, find the time to review their past mode of living, particularly that part of it immediately prior to the onset of their infarction. During such reflection many of these patients begin to comprehend that even though they had ingested a diet low in cholesterol but rich in unsaturated fat, had not smoked, had suffered from neither hypertension nor diabetes, and had engaged in regular vigorous exercise, nevertheless they had developed an infarction.

Such thoughts of course suggest to such patients that the many articles they previously had read and also the counsel that they had received from their physicians obviously had not taken into account some "other risk factor." And the possible identity of this "other risk factor" becomes overwhelmingly important to these post infarction patients because they retain sufficient common sense to intuit that it was precisely this "other risk factor" that had precipitated their own acute infarction.

In trying to ferret out this "other risk factor" they reluctantly but inevitably face up to the probable fact that it is some form of emotional stress. And it is at this time that they recall how often they had been warned by the members of their family or by friends prior to their acute infarction that they had been "driving" too hard and too relentlessly. Indeed some of these convalescent patients resolve of their own volition that they never again will try to achieve so much in so little time. But whether or not they so resolve, it is this sort of introspection that makes them far more susceptible to later alteration of their Type A behavior.

A second reason that the Type A behavior pattern in post infarction patients is more tractable to alteration is that such patients no longer can fool themselves by supposing that Type A behavior may bring on ischemic heart disease in other persons but not in themselves. They have received a dreadful denial of their self-assumed immunity. They no longer wish to depend upon their "luck" in this regard.

A third reason that Type A post infarction patients frequently are amenable to behavior modification is that they frequently experience frightening symptoms (e.g., angina, dyspnea, easily induced fatigue) if they indulge in activities compelling them to struggle either against the clock or against other persons. Accordingly adherence to a regimen designed to modify their Type A behavior frequently precludes the occurrence of some of their previous symptoms. The therapist then can offer to post-infarction patients therapeutic rewards following modification of behavior which cannot be offered to the symptomless and seemingly well Type A persons.

B. Selection of post-infarction patients amenable to alteration of Type A behavior. It is important before attempting to modify Type A behavior in post-infarction patients[2] to determine in such patients whether (1) both components of Type A behavior are present, and (2) the degree of severity of each component. This usually can be easily accomplished by giving the patient a standardized structured interview taking approximately 15 minutes.

The interview chiefly serves as a period during which the examiner can observe the patient's psychomotor manifestations (see Table I) and his

[1] It should occasion no surprise that many of the cardiologists who now believe that Type A behavior is essentially unmodifiable are precisely the same cardiologists who a decade earlier rejected the probable role of Type A behavior in the pathogenesis of clinical ischemic heart disease.

[2] At least 80 per cent of infarction patients under the age of 65 years exhibit Type A behavior. Although we observed in our prospective epidemiological studies, that ischemic heart disease did occur in a number of subjects whom we had assessed in 1960-61 as exhibiting Type B behavior, I now believe that if we had known then what we now know about the detection of Type A behavior, almost every one of these men in 1960-61 would have been labeled Type A. This is because almost half of the psychomotor manifestations we now employ for the detection of either of the two components of Type A behavior (see Table I) have been discovered only in the last decade.

Table I Diagnostic indicators of Type A behavior

I. Time urgency (Component 1)
Psychomotor manifestations
1. Characteristic facial tautness expressing tension and anxiety
2. Rapid horizontal eyeball movements during ordinary conversation
3. Rapid eye blinking (over 40 blinks/minute)
4. Knee jiggling or rapid tapping of fingers
5. Rapid, frequently dysrhythmic speech involving elision of terminal words of sentences
6. Tongue to front teeth clicking during ordinary speaking

Direct behavioral tests (Questions to be interspersed during entire interview)
7. The interviewer in posing a question whose answer is already clear from context, hesitates, becomes laboriously tedious or repetitive, and then stammers. Does the subject interrupt with his answer?
8. Same procedure but a second question is employed
9. Same procedure but a third question is employed

Significant biographical content
10. Subject reports that he engages in polyphasic activities (e g dictates while driving, reads while using electric sha er etc.)
11. Subject reports that during conversation with others, he also thinks about other matters, rarely giving the other person his undivided ttention
12. Subject reports that he eats and walks fast and does not like to dawdle at table after eating
13. Subject makes fetish of al ays being on time under all circumstances
14. Subject reports that he finds it difficult to sit and do nothing
15. Subject reports that his wif has told him to slow down in his working and living habits
16. Subject habitually substitutes numerals for metaphors in his speech

Table I Cont d

II. Hostility (Component 2)
Psychomotor manifestations
1. Characteristic facial set exhibiting aggression and hostility (eye and jaw muscles)
2. Characteristic tic-like drawing back of corners of lips almost exposing teeth
3. Hostile, jarring laugh
4. Use of clenched fist and table pounding or excessively forceful use of hands and fingers
5. Explosive, staccato, frequently unpleasant sounding voice
6. Frequent use of obscenity
7. Subject exhibits irritation and rage [illegible] about some past events in which he became angered

Direct behavioral tests
8. The interviewer directly challenges the [illegible] of some comment or behavior that the subject has reported. Does the subject react in a hostile or unpleasant manner?
9. The interviewer questions the subject about his views on politics, races, women, competitors. Does subject respond with absolute [illegible] most angry generalizations?

Significant biographical content
10. The subject reports his easily aroused [illegible] tilities if kept waiting for any reason or if driving behind a car moving too slowly in his view
11. The subject expresses general distrust of other people motives—e g, distrust of altruism
12. The subject reports that he almost al[illegible] plays any type of game (even [illegible] his young children) t win

reactions to direct behavioral tests (Table I) However as Table I indicates, the interviewer also attempts to obtain certain biographical details that may carry diagnostic relevancy But one note of caution Unless a patient either exhibits one or more psychomotor manifestations or reacts positively to one or more of the direct Behavioral Tests, the diagnosis of Type A behavior probably should not be made [illegible]gardless [illegible] the biographical content [illegible] *In other words the final diagnosis of Type A behavior primarily depends upon th[illegible] detect[illegible] tion or elicitation of object[illegible] phen[illegible]*

Let me emphasize, however that few Type A subjects show *all* the psychomotor manifestations or respond positively to all the behavioral tests or relate a complete set of biographical indicators as listed in Table I Thus perhaps only one of 20 Type A subjects may exhibit rapid eye blinking; one in 10 knee jiggling; or one in [illegible] tongue to front teeth clicking, etc. Nevertheless if only one of these signs is observed during an interview the physician should strongly suspect that Type A behavior may be present. Of course Type A subject rarely only exhibits one or two of the diagnostic indicators listed in Table I. Usually half the indicators of each of the three listed categories will be observed during the 15 minute structured interview

In my experience, if a post infarction patient exhibits a severe degree of hostility (i e if he exhibits most of the psychomotor manifestations responds positively to the direct behavioral tests and admits the presence of the biographical m[illegible]

cators listed in Table I) it is very difficult to modify not only this component but the severe sense of time urgency that such a patient also almost always exhibits.

I don't know precisely what percentage of post infarction patients will *exhibit such severe* hostility. But I should guess that perhaps 20 to 30 per cent of any series of successively encountered r ... nfarction patients might show it. Certainly ... say this. The younger the age at which ... on occurs, the more severe the hostility ... nt usually will be found to be. This, of ... nplies that in the age range of 30 to 65 ... younger the post infarction patient is, ... ifficult it will be to modify his Type A ... id unfortunately this is exactly what ... rienced.

... tion patients are also encountered ... behavior may not be significantly ... hough neither of the two compo- ...) their Type A behavior may be ... m a second type. They are ... ral intelligence is of such poor ... nnot truly comprehend most ... dealing with abstract, figu ... entities. This handicap ... ons from understanding the ... effective therapy requires. More ... d, only words correctly formulated, received, understood, and then acted ... ne patients can be employed in attempt ... modify Type A behavior. Neither the ... pel nor a drug can achieve this modification.

However, I believe most post infarction Type A patients are amenable to behavior modification. As already intimated, the behavior pattern of older patients is more easily modifiable. Also, if the post infarction Type A subjects display a more severe degree of sense of time urgency than free-floating hostility, their behavior pattern usually can be more easily altered. Also if patients have worked in or been exposed to a milieu that encouraged the emergence or intensification of the Type A behavior, their Type A behavior *may be more easily changed*. I have found this to be true because *Type A behavior frequently emerges only after a particular personality (Type A personality) is exposed to and reacts to certain provocative challenges or stimuli arising from the milieu.* This is an important fact to remember because in some cases, Type A behavior cannot be successfully modified unless the subjects exhibiting this behavior avoid or learn to reinterpret the meaning, relevance, or significance of certain factors in their milieu.

The Type A behavior of post infarction patients who are not totally egocentric in their relations with other individuals is still amenable *to change*. It is almost axiomatic that the more truly interested post infarction patients are in things, events, and persons which are not extensions of their own self interests, the easier it will be to modify their Type A behavior. Certainly one of the most hopeful signs of patients' progress in changing their behavior is their increasing capacity to take a keen and active interest in activities that bear no direct relation with those of their own. On the other hand, if the therapist notes that the patients' attentions and interests inevi*tably and very quickly return to their own partic*ular preoccupations regardless of the intrinsic merit, interest, and importance of other phenomena presented to them, he can conclude that little modification of behavior pattern has yet been accomplished. In a very real way, the egocentrism of Type A subjects is what encapsulates their sense of time urgency and their free-floating hostility and makes their alteration so difficult to achieve. Therefore this encapsulation when discerned must be ruptured.

Finally, Type A patients most amenable to alteration in behavior are those who not only suspect that something has gone awry in their *personality and in their way of living, but* who sincerely wish to do something about it. Peculiarly, post-infarction patients of this sort are not a rarity. But what happens to these persons is that when they seek such aid from their cardiologists, they find the latter quite inadequate as guides for behavior modification. As a consequence, the majority of them continue in their dangerous habits of feeling and doing. A few, however, entirely on their own, seek and eventually find a modicum at least of tranquillity. And tranquillity, *of course, is the converse of* Type A *behavior*.

C. Alteration of Type A behavior in post infarction patients.

1. The necessity of motivation. Before I list procedures I have found useful in modifying Type A behavior, let me say at the outset that post infarction patients will not attempt to alter their Type A behavior unless they are strongly motivated to do so. And they cannot be so motivated by a physician warning them that unless they modify their behavior, they may *suffer a second*

heart attack. Indeed such a warning may prove to be directly counterproductive. Why is this so? Because many of these patients long before they suffer their acute infarction have harbored what has to be called a Freudian type of death wish.

What then can the physician do to motivate post infarction patients to begin a regimen aimed at altering their Type A behavior? He must do two things. First, he must convince such patients that both their sense of time urgency and their free-floating hostility were not responsible for whatever past successes they may have achieved, but on the contrary probably were directly responsible for any failures that these patients had experienced. Also the patients must be shown that either or both of the Type A components possibly could have restricted the extent of those past successes that they had secured.

The majority of Type A post infarction patients must be so convinced because they have been accustomed to attribute to their sense of time urgency (i.e., their impatience) and their free-floating hostility (i.e., their easily aroused irritability and anger) responsibility for whatever success and socio-economic security they have obtained. Of course this is a false attribution in most cases, because whatever successes and security these patients have gained for themselves, have been obtained primarily because of their possessing such qualities as good judgment in decision making, formulation of original, creative ideas in their industrial, commercial, or professional lives, or reliability or integrity or good salesmanship, etc. It is absolutely necessary that the physician instruct his post infarction patients concerning the true role these latter attributes played in their successes, and it is instruction that must be repetitiously administered over a period of many months.

This is necessary because it is not easy for the therapist to convince individuals that a behavior which these individuals previously had identified as the capstone of their past socioeconomic efforts actually will be the lodestone for whatever future failures and frustrations they may encounter. But it is not a hopeless task to get even Type A post infarction patients to recognize a truth. They just require quite a long time to acquire this capacity.

The second step that the therapist can take to motivate post infarction patients to begin attempts at modifying their Type A behavior is to identify for such patients those facets of their personality which they have lost in their increasing subservience to the frenetic demands of their Type A behavior but which they still can regain. Frequently post infarction patients are not aware of the fact that their many years of hurry sickness[1] and free-floating hostility gradually have stripped them of their former capacities to enjoy slow paced, amiable, and warm but non goal directed social intercourse with old friends; to read leisurely and happily worthwhile books and magazines, to attend with interest and even excitement concerts, the theatre, and the museums, to find joy and relaxation in one or more avocations, or to employ a variety of metaphors both in their oral and written communications with friends and acquaintances.

Revelation of this increasing impoverishment of their total personality almost always comes as a shock to Type A post infarction patients. This is particularly the case if such patients outwardly appear rather proud of their socioeconomic or professional achievements. But when the attention of these patients is directed by the therapist to this intrinsic poverty of their general personality irrespective of their wordly status, they will sadly agree that such impoverishment exists. They also will agree that any step that may reverse this *degenerative* process should be taken.

These then are the two steps that I have found must be taken to *motivate* post-infarction patients to attempt to rid themselves of some of the most noxious aspects of Type A behavior. Certainly if such patients can be shown and convinced that a behavior pattern to which they had falsely attributed their past successes actually had probably hindered their career and certainly had plundered their personality, they subsequently will be amenable to counsels designed to alter this same behavior pattern. I cannot stress

Although I had perceived this inclination in [illegible] number of post infarction patients and also in perfectly [illegible] but severe Type A subjects, this psychiatric aberration and its possible relation to coronary heart disease [illegible] was not described in either of our [illegible] monographs describing Type A behavior because of its resistance to quantitative description. However several unusually astute laymen who have suffered acute infarctions have criticized us (and I believe on fair grounds) for our failure to include this emotional tendency. At first glance, of course, the presence of an unconscious drive for death in [illegible] group of subjects [illegible] appear so eager and desirous for indefinite living struck me as paradoxical [illegible] still does, [illegible] I now am certain that such [illegible] is present in many post infarction patients. It certainly must be reckoned [illegible] any measures dealing with compliance are being considered.

too strongly that *unless this motivation is not only secured but is also constantly maintained* any physiological or psychological procedure designed to ease or abolish the emotional stresses and strains engendered by Type A behavior inevitably will prove useless. This is because all such procedures to be successful require the subjects continuing interest and participation and this is precisely what *unmotivated* Type A post infarction patients will not give to such procedures. This homely truth is apt to be forgotten by therapists whose interests are attuned more to the techniques they attempt to employ than to the reactions of their patients.

2. Introduction of philosophical and spiritual values. I believe it is obvious that the motivation for change of behavior as just described heavily depends upon a series of discussions with post infarction patients that are composed essentially of philosophical and even spiritual ingredients. I know that today few medical committees or panels care to waste time discussing such unquantifiable, scientifically nebulous entities as philosophical and spiritual problems. Knowing this reluctance of some of my medical peers to take seriously any therapeutic regimen that entails philosophical and spiritual matters, I long have hesitated to declare that which my 15 years of experience in trying to alter Type A behavior increasingly has made clear to me, namely that subjects severely afflicted with this disorder are *spiritually* ill. I also might add that I can't remember ever treating a Type A post infarction patient who finally didn't admit that he harbored this defect.*

Indeed even scientists (and I know physicians also are not immune) can fall victim to this peculiar spiritual malaise. For example, Charles Darwin discovered that he had lost some of the "things worth being" in his quest for the things worth possessing (e.g., fame in his case) when in middle age he attempted and found he could not *return to the reading of poetry and the enjoyment* of looking at fine paintings. Saddened by this discovery he wrote

"My mind seems to have become a kind of *machine* for grinding general laws out of large collections of facts but why this should have caused the atrophy of that part of the brain alone on which the higher tastes depend, I cannot conceive. The loss of these tastes may possibly be injurious to the intellectual and the moral character by enfeebling the *emotional* part of our nature."

I don't believe even Darwin would have objected too violently if I substituted the word "spiritual" for "emotional" in this quotation.

In order to aid post infarction patients rediscover and restore certain philosophical and spiritual values in their lives, the therapist's efforts must transcend the usual limits of ordinary medical care. The particular measures that I have found useful to aid Type A post infarction patients rediscover and restore certain philosophical and spiritual values to their daily living are described in considerable detail in one of our recent publications.[14] I would strongly recommend the perusal of this book to any physician who is interested in modifying the Type A behavior of his post infarction patients. Suffice it to state here that patients must receive specific and explicit instructions how to first re-evaluate their past material, as well as abstract, accomplishments and then to reconstruct a new mode of living in which such abstractions as friendship, affection, and joy will serve as the new foci for many of their activities. Obviously these latter changes cannot take place in a day, a week, or even in a month. But I have observed that eventually they can and do take place. I also have observed that if they don't, no significant or permanent alteration in behavior pattern ever ensues.

3. Restructuring of daily events. Although a philosophical and spiritual change is requisite for behavior modification, if only this is accomplished, Type A post-infarction patients still may suffer intensely from the struggle that their sense of time urgency constantly induces. Thus, I have treated several monks whose Type A behavior stemmed not from any defect in their philosophical or spiritual values but from their almost demonic drive to accomplish *far too many things* in far too little time.

In other words, the daily schedule of post infarction patients must be altered so that they consistently allow themselves enough time to perform tasks so that they rarely feel themselves at any part of the day being pushed for want of time. This, of course, almost always demands that the patients arbitrarily cut down the number of

*This admission generally comes from patients after they have made considerable progress in modifying their pre-infarction Type A behavior.

activities that they previously had pursued each day. Frequently this may mean the resignation from various committees, clubs, and organizations, less involvement in community, social, or sporting events or even less activity in the patient's own business or profession.

Indeed in a few instances, I believe that behavior change cannot be accomplished unless some patients do resign or retire from their preinfarction vocations. For example, it is difficult for me to see how a post infarction patient who has been a city editor or a television producer or director can return to these same jobs and still easily alter his behavior. Fortunately, the vast majority of jobs and positions are not nearly so conducive as these two to the development of a sense of time urgency.

The physician as the counselor in this restructuring process must stand firm in urging an elimination of various activities previously participated in by his patients regardless of the possible resistance put up by these same patients. I say this because the majority of Type A post infarction patients do not relish adopting a regimen which they sometimes describe as "doing less and less in more and more time." Most of them have indulged in this struggle against time for decades and it has become not only a habit but a way of life which they had regarded as an eminently respectable and praiseworthy one. Thus it is not only difficult for them to break free of this habit, it is also difficult for them not to feel guilty when they are simply resting at any period during the hours of their working period.

4. Abatement of free floating hostility. It is the presence of this emotional trait and the addictive satisfaction it appears to provide persons afflicted with Type A behavior that, more than any other trait exhibited by them, has made me suspect that a spiritual deficit may play a part in the evolution of this type of behavior.

Certainly of the two components comprising Type A behavior, the most difficult one to treat as I already have intimated is that of free floating hostility. Indeed as I've already indicated, if this component is stron[illegible] entrenched and obviously influencing the dail[illegible] activities [illegible] its possessor it is unlikely that it [illegible] can be significantly lessened. F[illegible]rtunatel[illegible] whil[illegible] the majority of post infarction pati[illegible] those under 60 years of [illegible] with

this emotional trait, the latter's intensity [illegible] is not overwhelming.

Here again, the physician's therapeutic [illegible] must depend not upon drugs but upon his [illegible] counseling of his patients how to amelior[illegible] severity or even how to rid themselves [illegible] personality blighting trait. Such counseling [illegible] effective requires not only expertise b[illegible] patience, because the patient possessing th[illegible] has been accustomed perhaps for dozens of [illegible] to rationalize, hence to excuse both its [illegible] existence and its overt discharge. Accordin[illegible] does not easily accept any counseling [illegible] suggests that his possession and frequent e[illegible]tion of a free-floating hostility is due to [illegible] error in his own makeup. Yet if he is to [illegible] himself from the destructive influence of [illegible] component of Type A behavior he finally [illegible] recognize that whatever may have been the [illegible]inal cause for its emergence, it now [illegible] sustaining and even worse, self-enhancing!

The necessarily slow process whereby the [illegible]apist instructs patients exhibiting this ch[illegible] form of hostility in measures that will less[illegible] intensity includes a number of procedures th[illegible] already have described in detail in a pre[illegible] publication.[34] Such procedures have as [illegible] object (1) the recognition by the patient of [illegible] true nature of this trait, (2) the circumst[illegible] that he should avoid in order to prevent [illegible] exhibition, and (3) the substitution of acts [illegible] affection and love for the sort of emotio[illegible] vacuum that results when the patient no l[illegible] has recourse to outbursts of anger or irrita[illegible] over essentially trivial matters.

5. The necessity for drill. Much, perhaps [illegible] of the sense of time urgency suffered by almo[illegible] Type A post infarction patients probably d[illegible] not have a genetic cause. Rather it more pro[illegible]bly develops in persons who either are forced b[illegible] others or who for divers reasons have f[illegible] themselves to constantly accelerate their pace [illegible] carrying on their usual daily activities. Acc[illegible]ingly, it is quite probable that the speed [illegible]

A harrowing example of how [illegible] sense of time urgency can be [illegible] [illegible] person can be found in E. Tarkel [illegible] description of the [illegible] [illegible] of an English Lt. Major [illegible] he becomes [illegible] [illegible] [illegible]. Nevertheless, reading of how [illegible] of [illegible] [illegible] of urgent events led to this girl [illegible] acquiring Type A [illegible] [illegible] rather comforting to me. Because it suggested that what [illegible] be [illegible] and enhanced by drill, also could be [illegible] [illegible] even abolished by [illegible] different sort of drill.

which most Type A post infarction patients think, talk, eat, walk, etc., has resulted from years of drilling in accelerating all those processes which appear capable of being hastened. Likewise the inveterate habit of these same patients to attempt to do two or more things simultaneously probably develops after years of "drilling" at this proclivity

It is also not too unlikely that the emergence of one outburst of hostility makes it easier for the later emergence of another similar outburst. In other words, like a sense of time urgency free-floating hostility also may be enhanced by drill.[4]

But regardless of the origins of either of these components, I know from my own experience that in order to modify Type A behavior in post infarction patients, they must be instructed to embark upon a daily regimen in which they indulge in a "drill" whereby they begin (1) to decelerate their usual pace of physical and intellectual activities and (2) to substitute on a conscious basis, affection and tolerance as their responses to events that previously had elicited their hostility Again, these measures are described in considerable detail in our previous publication.[4]

6. *The importance of the physician's personality* I already have emphasized how important a role motivation on the part of post infarction patients plays in any attempt to modify their Type A behavior Yet acquiring this motivation requires a particular kind of therapist one who either does not possess Type A behavior himself or if he does possess it, recognizes its presence and is *actively* trying to modify or blunt its force in his own living patterns. Once again one group of blind men cannot be led successfully by another group of blind men, even if the latter also are cardiologists. What I am saying, of course, is what Blankenhorn and associates[5] have intimated A cardiologist who himself suffers from a severe case of Type A behavior and makes no attempt to diminish its severity cannot and should not attempt to abolish this risk factor in post infarction patients, because he cannot convince others to make changes which he cannot or does not choose to effect in his own living.

Fortunately however a therapist does not need certification in cardiovascular disease in order to attempt modification of Type A behavior Indeed, the therapist doesn't necessarily need any sort of degree for successful modification of Type A behavior What he does need, however is a cognitive and emotional awareness of the presence, the character the depth of penetration into the personality of Type A behavior and the probable forces that gave rise to and are sustaining the continued existence of this disorder. He also must possess a relatively full faceted personality of his own so that it will be very easy for him to proffer affection along with his instructions to post-infarction patients. I say that because if post-infarction patients find that they cannot wholeheartedly admire, trust, and feel affection for their therapist, they are not very likely to venture forth on the *initially* stony path of behavior modification. Indeed, I know of no other disorder whose successful treatment requires a closer bond to exist between physician and patient.

Addendum

Since the submission of this manuscript, a Review Panel of distinguished investigators was assembled on December 4, 1978, by the Director of the National Heart, Lung & Blood Institute to review the evidence suggesting a possible association between Type A Behavior Pattern and an increased risk of clinical coronary heart disease. The Review Panel, after three days of intensive deliberation, concluded that the available body of scientific data suggested that there was an association between increased risk of clinical coronary heart disease and Type A Behavior Pattern. They further concluded the increased risk is over and above that imposed by age, systolic blood pressure, serum cholesterol and smoking and appears to be of the same order of magnitude as the relative risk associated with any of these other factors.

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Mitral valve prolapse in adults with congenital heart disease

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During the 15 years since Barlow and associates demonstrated that the click-murmur syndrome could be explained by mitral valve prolapse, the syndrome has continued to spark considerable interest. Barlow and colleagues[1] initially suggested that the syndrome could arise from diverse etiologies. Recent angiographic and echocardiographic studies have confirmed this suggestion, greatly expanding the list of possible etiologies and conditions associated with mitral valve prolapse.

The association between atrial septal defect and mitral valve prolapse (MVP) was noted in Barlow's initial group of patients, and was elaborated by subsequent investigators.[2-8] Pocock and Barlow[9] also reported mitral valve prolapse associated with other congenital lesions including Eisenmenger's syndrome (one case) and patent ductus arteriosus (one case) without noting an increased incidence of prolapse in these conditions. Recently Ebstein's anomaly has been added to the list of congenital lesions with associated mitral valve prolapse.[11] Questions remain concerning the spectrum of congenital diseases in which mitral valve prolapse occurs, the frequency of prolapse, possible etiologic links between the two entities, and the natural history of the combined lesions.

During the past three years, echocardiograms have been performed at the Peter Bent Brigham Hospital Heart Station on 120 adults with congenital heart disease, comprising virtually all patients with congenital heart lesions seen at the Peter Bent Brigham Hospital during this period. Mitral valve prolapse was present with surprising frequency in this group, with 40 documented cases (34 per cent of the entire group): ASD secundum, nine cases; VSD, 10 cases; PDA, five cases; tetralogy of Fallot, three cases; Ebstein's anomaly, two cases; and miscellaneous congenital heart lesions, four cases. We report these 40 patients and discuss possible etiologic links and clinical relevance.

Materials and methods

Echocardiograms were examined from 120 adults with congenital heart disease studied in the Peter Bent Brigham Hospital Heart Station between December 1, 1974, and December 1, 1977. Since a large children's hospital, Children's Hospital Medical Center, is located in close proximity to the Peter Bent Brigham, children are rarely examined at our hospital, and no individual under the age of 17 is included in the present series.

Forty patients (20 males and 20 females) ranging in age from 17 to 57 years, were found to have mitral valve prolapse. They had been referred for a variety of reasons. Many had been followed for congenital heart defects since childhood and had reached a point where definitive correction was felt to be necessary. Others had undergone repair of congenital defects as children, and were receiving routine periodic follow-up. Some patients were studied as part of regular care for lesions not considered significant enough to require surgical intervention. Finally, a small group of patients

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Table I Prevalence of mitral valve prolapse with each type of congenital heart disease

Type of CHD	Total no studied	No. with associated MVP	% with associated MVP
ASD II	32	9	28%
ASD I	5	0	0%
VSD	25	10	40%
PDA	7	5	71%
TOF	5	3	60%
PS	15	5	33%
Congenital LV outflow obstruction	14	2	16%
Ebstein anomaly	3	2	67%
Miscell neou	14	4	29%
Totals	120	40	33%

with abnormal cardiac examinations were studied and were found to have previously undiagnosed congenital lesions. None of the 40 patients was initially referred for evaluation of possible mitral valve prolapse.

The diagnosis of congenital heart disease was confirmed by cardiac catheterization in the majority of patients with hemodynamically significant disease In the remainder the diagnosis was established by clinical evidence with supporting noninvasive examinations. The diagnosis of mitral valve prolapse was made by established echocardiographic criteria. All of the patients exhibited the characteristic pattern of posterior buckling or bulging of the mitral valve apparatus during systole and displayed either late systolic bowing" or holosystolic hammocking

Echocardiograms were obtained using standard techniques and were recorded on commercially available Irex or Smith Kline recording devices interfaced with Irex strip chart recorders and 2.25 or 3.5 MHz transducers.

The mitral valve was visualized in standard views with particular care exercised to avoid pseudo prolapse or inferior angulation of the echo transducer which might alter the apparent location of the mitral valve

Results

a ASD secundum Of 32 patient with ASD secundum studied nin (28 per [illegible] cated mitral valve prolapse (Tabl I) [illegible] nine also had anomalou pulr [illegible] drainage while the remaining eight patients had ASD secundum without associated anomalies Eight of the nine patients had experienced at least mild shortness of breath or fatigue while only two were troubled by chest pain. Palpitations occurred in five of the nine patients ([illegible] per cent) None had contracted SBE (Table II).

Physical examination prior to surgical intervention revealed murmurs typical of ASD in eight of nine patients (89 per cent) the only exception being a patient whose ASD had been repaired. A murmur compatible with the click-murmur syndrome was heard in only one patient (11 per cent) In this patient, a mid-systolic click was noted on one physical examination and was confirmed by phonocardiography

Electrocardiograms were typical for ASD with either complete or incomplete right bundle branch block in all nine patients. In addition RVH was present in four patients, and nonspecific ST and T wave abnormalities were present in three patients.

On echocardiogram, both holosystolic and late systolic mitral valve prolapse were observed (Fig. 1)

Surgical correction, undertaken in six of the nine cases (one patient had previously undergone surgery) was completed without complications or postoperative difficulties in any instance. No gross abnormalities of the mitral valve were noted at surgery although its examination was limited.

b ASD primum There were five patients with ASD primum examined during this period, and none had evidence of mitral valve prolapse. All showed typical features of ASD and endocardial cushion defects.

c. VSD Twenty five patients with VSD were studied and ten (40 per cent) were found to have associated mitral valve prolapse (Table I). Two of these ten had other congenital cardiac anomalies in addition to VSD (one pulmonic stenosis, and one peripheral pulmonic stenosis) while the remaining eight had isolated VSD In six individuals with larger defects, the diagnosis was confirmed by catheterization, while four patients had the diagnosis of a small VSD made clinically Five of the ten patients (50 per cent) had symptoms of congestive failure two had chest pain, and four had experienced palpitations. A question of SBE was raised in one instance (for a fever of unknown origin) This patient was treated with high dose

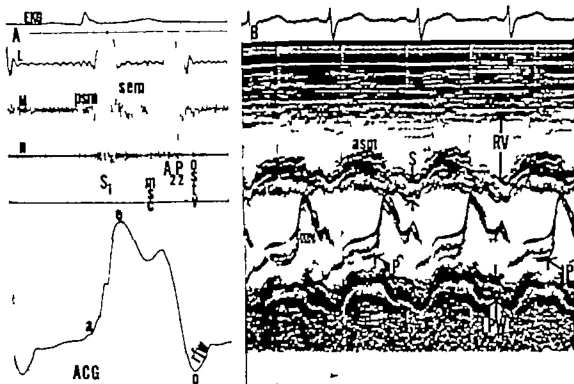


Fig. 1 Patient with atrial septal defect and mitral valve prolapse. *A*, Apex phonocardiogram and apexcardiogram (*ACG*). There is loud mid-systolic click (*MSC*) as well as one or two clicks toward end systole which are unlabeled. Also recorded are typical auscultatory findings of pre-systolic murmur (*PSM*), systolic ejection murmur (*SEM*), and tricuspid valve opening sound (*OSTV*), as well as faintly recorded flow rumble (unlabeled) following OSTV. *L* = low frequency; *M* = mid frequency; *H* = high frequency; *RFW* = rapid filling wave. *B*, Echocardiogram of the mitral valve at the base of the left ventricle. There is late systolic prolapse (*P*) of the mitral valve (*MV*). Also seen is an enlarged right ventricle (*RV*) and abnormal anterior systolic motion (*ASM*) of the septum (*S*).

intravenous antibiotics, although no organism was isolated. Physical examination revealed the holosystolic murmur of VSD in eight of ten cases (the two exceptions had undergone surgical repair). A mitral regurgitant murmur was heard in only one instance, and no patient had a mid-systolic click (Table II).

Electrocardiograms were normal in six of the ten patients, RVH or LVH was present in two, VPCs in one, and non-specific ST and T wave abnormalities were present in one. Chest x rays were normal in the majority of these patients.

On echocardiogram, in addition to MVP, LV volume overload was often noted. In one patient with a large, subaortic VSD aortic overriding of the large defect was noted. The pattern of mitral valve prolapse was variable, and not different from the usual pattern (Fig. 2).

Surgery was performed in two instances. In one patient a new aortic regurgitant murmur was heard three months postoperatively, subsequently found to be due to a perforation of the aortic valve.

d. **Patent ductus arteriosus.** Seven cases of this entity were examined, and five were found to have associated mitral valve prolapse (71 per cent). Four of the five patients (80 per cent) had symptoms of CHF, none had chest pain, three had palpitations, and none had suffered SBE (Table II).

On physical examination, four of the five patients had typical continuous "machinery" murmurs before surgical correction. In one case with associated pulmonary vascular obstruction a systolic murmur of tricuspid regurgitation was heard, while in two patients, murmurs of mitral regurgitation were heard. In one of these cases, a mid-systolic click was also present on physical examination, and was confirmed by phonocardiography (Fig. 3).

Electrocardiograms were dominated by LVH, which was present in three of the five tracings,

Table II Clinical data Congenital heart disease and mitral valve prolapse

						Historical data				Physical exam.			Lab data		
Patient No	Initials	Hospital No.	Sex	Age	Type of congenital heart disease	Symptoms of CHF	Chest pain	Palpitations	SBE	Clicks	Murmurs	Marfans Habitus	ECG	Cath	Su[illegible] ge[illegible]
Atrial septal defect (secundum)															
1	RM	282143	M	38	ASD II with anomalous pulm venous drainage	+	–	+	–	–	II/VI ASD	–	LAE, 1° AV block; RBBB LAAB	+	+
	MP	282215	F	40	ASD II	+	–	–	–	–	II/VI ASD	–	inc RBBB, RVA	+	+
3	DA	241109	F	43	ASD II	+	–	–	–	–	II/VI ASD	–	inc. RBBB, NSST	+	
4	RK	186434	M	49	ASD II	+	–	+	–	–	II/VI ASD	–	1° AV block inc. RBBB	–	
5	RL	266609	F	25	ASD II	+	–	–	–	–	II/VI ASD I/VI dias.	–	inc. RBBB		+
6	LL	274738	F	28	ASD II	+	–	+	–	–	III/VI ASD I/VI dias.	–	inc RBBB	+	+
7	PO	285203	F	30	ASD II	+	–	+	–	–	–	–	inc RBBB NSST	–	+([illegible]
8	JH	205971	F	43	ASD II	+	–	+	–	–	III/VI ASD	–	inc. RBBB RVH	+	+
9	NN	271608	F	30	ASD II	–	+	–	–	–	III/VI ASD	–	inc RBBB RVH	+	+
Atrial septal defect (primum)															
None															
Ventricular septal defect															
10	AH	244180	F	22	VSD	–	–	–	probable (no organism)	–	II/VI VSD	–	sinus tachy	–	
11	HG	158619	M	25	VSD	+	+	+	–	–	III/VI VSD	–	WNL	+	
12	JF	282968	F	30	VSD	–	–	–	–	–	III/VI VSD	–	NSST	–	

Abbreviations AI = aortic regurgitation AS [illegible] stenosis A[illegible]D [illegible] septal defect COARCT = coarctation; DIAS = diastolic [illegible] 1° = first degree AV block, inc RBBB [illegible] incomplete right bundle branch block LAHB [illegible] left anterior hemiblock; LAE = left atrial enlargement LBBB = left bundle branch block LVH [illegible] left ventricular hypertrophy NSST [illegible] non-specific ST T changes, PDA = patent ductus arteriosus PR = pulmonic regurgitation, PS [illegible] pulmonic stenosis R[illegible]B[illegible] right bundle branch block RVH = right ventricular hypertrophy, sinus tachy = sinus tachycardia, TOF = tetralogy of Fallot [illegible] VPC's [illegible] ventricular premature beats, VSD [illegible] ventricular septal defect; WNL = within normal limits

Table II Cont'd

Patient No.	Initials	Hospital No.	Sex	Age	Type of congenital heart disease	Historical data: Symptoms of CHF	Historical data: Chest pain	Historical data: Palpitations	Historical data: SBE	Physical exam.: Clicks	Physical exam.: Murmurs	Physical exam.: Marfans Habitus	Lab data: ECG	Lab data: Cath	Surgery
Ventricular septal defect															
13	AE	246696	M	28	VSD pulmonary stenosis	–	–	+	–	–	I/VI VSD	–	WNL	+	+
14	SM	490753	M	21	VSD, peripheral pulmonary stenosis	+	–	–	–	–	II/VI VSD-II/VI PS	–	RVH, intraventricular conduct defect	+	–
15	KG	212306	F	24	VSD	+	–	–	–	–	IV/VI VSD	–	VPCs	–	–
16	RR	267122	M	30	VSD	–	–	+	–	–	III/VI VSD	–	WNL	–	–
17	FM	280426	M	30	VSD	+	+	+	–	–	IV/IV VSD	–	WNL	+	–
18	LS	242547	F	23	VSD	+	–	–	possible (no organism)	–	IV/VI VSD II/VI PR	–	LAE, LVH, RVH	+	+
19	DL	237620	M	24	VSD	–	–	–	–	–	III/VI VSD	–	WNL	+	–
Patent ductus arteriosus															
20	PC	254542	M	45	PDA	+	–	–	–	+	III/VI PDA	–	inc. RBBB LVH, RVH,	+	+
21	WS	222449	M	57	PDA	+	–	+	–	–	III/VI PDA	–	LVH w/ strain	+	+
22	MW	258451	F	48	PDA aneurysm	+	–	+	–	–	III/VI PDA	–	LAE	+	+
23	SA	226581	F	31	PDA	+	–	+	–	–	III/VI PDA	–	counter clockwise rotation	+	+
24	JL	219518	M	22	PDA	–	–	–	–	–	III/VI PDA II/VI TR	–	1° AV block LVH	+	+
Tetralogy of Fallot															
25	JC	270942	M	30	TOF	+	–	+	–	–	III/VI PS	–	LAHB RBBB	+	+
26	FL	210431	M	22	TOF	+	–	–	–	–	II/VI PS II/VI PR, II/VI VSD	–	LAHB RBBB, LVH. RVH	+	+
27	RM	067009	M	32	TOF	+	–	–	–	–	III/VI PR, VI/VI	–	LAHB RBBB; LVH, RVH	+	+

Table II Cont d

Patient No	Initials	Hospital No	Sex	Age	Type of congenital heart disease	Historical data: Symptoms of CHF	Historical data: Chest pain	Historical data: Palpitations	Historical data: SBE	Physical exam.: Clicks	Physical exam.: Murmurs	Physical exam.: Marfans Habitus	Lab data: ECG	Lab data: Cath	Surgery
Congenital pulmonary stenosis															
28	MK	262936	F	27	PS	+	–	–	–	–	III/VI PS	–	WNL	–	
29	LM	282406	F	34	PS	–	–	–	–	–	III/VI PS	–	WNL	–	
30	EC	264603	M	21	PS	–	–	–	–	–	V/VI PS		RVH w/ strain	+	+
31	SM	28.570	M	17	PS	–	–	–	–	–	III/VI PS	–	RBBB	–	
32	FC	183482	F	24	PS	+	–	–	–	–	I/VI PS	–	WNL	+	
Congenital left ventricular outflow obstruction															
33	SA	286360	M	27	Bicuspid Aortic Valve	–	+	–	–	–	I/VI AS II/VI AI	–	WNL	–	
34	TR	006753	M	24	Repaired coarct bicuspid aortic valv	+	–	–	–	–	I/VI AS; II/VI AI	–	WNL	–	
Ebstein anomaly															
35	LF	216347	F	30	Ebstein Anomaly	+	–	–	–	–	IV/VI AS IV/VI AI	–	WNL	–	
36	RC		M	23	Ebstein Anomaly	+	–	–	–	+	II/VI AS II/VI AI	–		–	
Miscellaneous															
37	JW	24.239	F	40	Peripheral pulmonary artery stenosis	–	–	–	–	–	III/VI continuous M	–	RVH	+	
38	DG	281.06	F	24	R paired stenosis of shunt	+	+	–	–	–	III/VI continuous M	–	RVH	+	
39	CC	278408	M	22	Tricuspid atresia	+	+	+	–	–	V/VI TR	–	Intra ventricular conduction defect	+	
40	LM	222720	F	2.	Idiopathic dilatation of pulmonary artery	–	–	–	–	–	II/VI PS II/VI PR	–	WNL	–	–

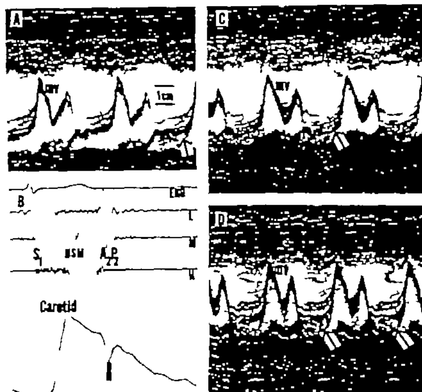


Fig. 2. Patient with ventricular septal defect and mitral valve prolapse. *A*, Echocardiogram of the mitral valve *(MV)* at rest. There is late systolic sagging *(unlabeled arrow)*. *B*, Left lower sternal border phonocardiogram and carotid pulse tracing. There is crescendo mid and high frequency holosystolic murmur *(HSM)* with normal carotid pulse. *L* = low frequency; *M* = mid frequency; *H* = high frequency; *DN* = dicrotic notch. *C*, Echocardiogram of the mitral valve during early Valsalva. There is more marked mitral valve prolapse (unlabeled) compared to the resting state. *D*, Echocardiogram of the mitral valve during late Valsalva. There is marked holosystolic prolapse of the mitral valve *(unlabeled arrows)*.

while conduction defects were present in two (incomplete LBBB and first-degree AV block). Cardiac catheterization, performed in four instances, confirmed the presence of PDA.

Echocardiograms showed dilated aortic roots and/or arches in three instances, left ventricular volume overload, and a spectrum of types of mitral valve prolapse.

Corrective surgery was performed in all five cases. There was one postoperative death in a patient who underwent emergency surgery to repair a ruptured ductal aneurysm and who died of complications 72 hours after surgery.

• **Tetralogy of Fallot.** Five patients with this anomaly were examined, all of whom had previously undergone at least partial surgical correction. In three cases (60 per cent) associated mitral valve prolapse was found (Table I). All three patients with prolapse had undergone complete repair of their tetralogy. All three had symptoms of congestive heart failure, none had experienced chest pain, one had experienced palpitations, and there was no patient with a history of SBE (Table II).

Physical examination showed residual pulmonic stenotic murmurs in two instances. There was one murmur of mitral regurgitation although no systolic clicks were heard.

Conduction defects predominated on the ECG with RBBB and LAHB present in all three cases. Biventricular hypertrophy was present in two instances. Preoperative cardiac catheterization had confirmed the diagnosis of Tetralogy of Fallot in all three cases. The echocardiograms performed as part of ongoing clinical follow-up showed a holosystolic pattern of mitral valve prolapse.

• **Congenital pulmonic stenosis.** Fifteen patients with this lesion were examined, and five had mitral valve prolapse (33 per cent) (Table I).

Table II Cont d

Patient No.	Initials	Hospital No.	Sex	Age	Type of congenital heart disease	Historical data: Symptoms of CHF	Chest pain	Palpitations	SBE	Physical exam.: Clicks	Murmurs	Marfans Habitus	Lab. data: ECG	Cath	Surgery
Congenital pulmonary stenosis															
28	MK	282936	F	27	PS	+	–	–	–	–	III/VI PS	–	WNL	–	
29	LM	282406	F	34	PS	–	–	–	–	–	III/VI PS	–	WNL	–	
30	EC	264805	M	21	PS	–	–	–	–	–	V/VI PS		RVH w/ strain	+	+
31	SM	285670	M	17	PS	–	–	–	–	–	III/VI PS	–	RBBB	–	
32	FC	183483	F	24	PS	+	–	–	–	–	I/VI PS	–	WNL	+	
Congenital left ventricular outflow obstruction															
33	SA	286360	M	27	Bicuspid Aortic Valve	–	+	–	–	–	I/VI AS, II/VI AI	–	WNL	–	
34	TR	006753	M	24	Repaired coarct bicuspid aortic valve	+	–	–	–	–	I/VI AS, II/VI AI	–	WNL	–	
Ebstein anomaly															
35	LF	215347	F	30	Ebstein Anomaly	+	–	–	–	–	IV/VI AS; IV/VI AI	–	WNL	–	
36	RC		M	23	Ebstein's Anomaly	+	–	–	–	+	II/VI AS II/VI AI	–		–	
Miscellaneous															
37	JW	245239	F	40	Peripheral pulmonary artery stenosis	–	–	–	–	–	III/VI continuous M	–	RVH	+	
38	DG	281905	F	24	Ruptured sinus of valsalva	+	+	–	–	–	III/VI continuous M	–	RVH	+	
39	CC	278408	M	22	Tricuspid trauma	+	+	+	–	–	V/VI TR	–	Intraventricular conduction defect	+	
40	LM	222720	F	25	Idiopathic dilatation of pulmonary artery	–	–	–	–	–	II/VI PS II/VI PR	–	WNL	–	

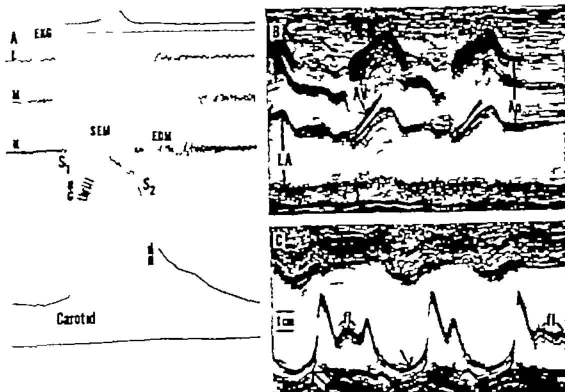


Fig. 4. Patient with repaired coarctation of the aorta, bicuspid aortic valve, and mitral valve prolapse. *A*, Left mid-sternal border phonocardiogram and carotid pulse tracing. There is crescendo-decrescendo systolic ejection murmur *(SEM)* of flow across the aortic valve, an early decrescendo diastolic murmur *(EDM)* of aortic insufficiency and prominent systolic ejection click *(EC)*. The carotid shows somewhat delayed upstroke and a systolic thrill. *DN* = dicrotic notch. *B*, Echocardiogram of the aortic valve. The leaflets are thickened and closure is asymmetric. *AV* = aortic valve; *A* = aortic root; *LA* = left atrium. *C*, Echocardiogram of the mitral valve. Anterior leaflet excursion is large. There is holosystolic mitral valve prolapse *(unlabeled arrows)*. Also seen is high frequency fluttering *(fl)* of the mitral valve consistent with aortic insufficiency.

h. Ebstein's anomaly. Three patients with this lesion were studied, and two had associated mitral valve prolapse (Table I). Both patients had experienced shortness of breath and fatigue, but neither had chest pain or palpitations. Neither had a history of SBE.

On physical examination both had systolic and diastolic murmurs heard at the left sternal border. One had multiple systolic clicks. The electrocardiograms showed only first-degree AV block. Echocardiographic data was consistent with Ebstein's anomaly with holosystolic mitral valve prolapse in both patients.

g. Miscellaneous congenital defects. Fourteen patients with a variety of other congenital defects were examined, and four (29 per cent) were found to have associated mitral valve prolapse. The spectrum of defects included in this category ranged from peripheral pulmonary artery stenosis to parachute mitral valve. The primary diagnoses of the four patients with echocardiographically demonstrated mitral valve prolapse were: peripheral pulmonary artery stenosis, ruptured sinus of Valsalva aneurysm with aorto-right heart communication, tricuspid atresia, and idiopathic dilatation of the pulmonary artery.

The clinical presentation varied considerably according to the underlying lesion. Two patients had experienced symptoms of congestive heart failure (one chronically and one acutely). Both of these patients had experienced chest pain, and one had also noted palpitations. Two of the patients were entirely asymptomatic. In the patient with ruptured sinus of Valsalva aneurysm, the question of SBE was raised but no organisms were isolated (Table II).

Physical examination revealed murmurs compatible with each of the primary diagnoses, although no clicks or late systolic murmurs were heard. Electrocardiograms were normal in two

instances, right ventricular hypertrophy was noted in one patient, and an intraventricular conduction defect was seen in the fourth. Cardiac catheterization performed in three instances confirmed the primary diagnosis. Echocardiographic data provided further confirmation. Several different patterns of prolapse were present.

Discussion

The use of echocardiography to diagnose and monitor both congenital heart disease and mitral valve prolapse is well established. An association between these lesions has been suggested since the earliest work of Pocock and Barlow and others. Pocock and Barlow's series, which contained examples of four types of congenital lesion combined with mitral valve prolapse, suggested that mitral valve prolapse might be linked to a variety of congenital cardiac anomalies, and raised the possibility of a common etiology. Despite subsequent demonstration of a high incidence of mitral valve prolapse in ASD secundum, evidence linking prolapse to other congenital anomalies has been scanty.

Recently mitral valve prolapse has been demonstrated to occur with considerable frequency among several groups of presumably healthy adults. The prevalence of mitral valve prolapse in patients with most types of congenital heart disease remains largely unexplored.

The association of mitral valve prolapse with various forms of congenital heart disease The association between ASD secundum and mitral valve prolapse has been well established. After Pocock and Barlow's, and Hancock and Cohn's initial suggestions of the association, numerous studies have confirmed the link. By 1974 there were over 60 reported cases in the world literature. In our current series, nine of 32 patients (40 per cent) with secundum ASD had associated mitral valve prolapse (Table I), an incidence similar to previously reported data. However in only one of these patients was the diagnosis of prolapse clinically suspected, a much higher incidence of silent mitral valve prolapse with ASD secundum than previously noted. Although none of these patients suffered from palpitations, and there were no cases of SBE, it might be argued that a higher incidence of cardiac symptoms was found in these patients than would be expected in ASD alone. The ECG changes which occurred can all be attributed to the atrial septal defect.

The absence of mitral valve prolapse associated with primum ASD is not surprising since the defect tends to limit motion of the mitral valve.

Ventricular septal defect with associated mitral valve prolapse has received far less attention than second degree ASD, a somewhat surprising fact in view of our finding that prolapse is at least as common in VSD (40 per cent) as in second degree ASD (28 per cent). Although Pocock and Barlow listed one case of mitral valve prolapse associated with Eisenmenger's complex, we are unaware of further documentation other than the ten patients in our series. Just as in the patients with ASD and MVP, none of these patients was recognized as having prolapse on clinical grounds. Two of the ten patients did have histories suggestive of SBE. Since this is a recognized complication of VSD as well as the MVP, its significance is difficult to evaluate. Electrocardiograms in patients with significant shunts were once again compatible with VSD without mitral prolapse.

Five of the seven patients with patent ductus arteriosus examined in our series had associated mitral valve prolapse, a strikingly high incidence. Although Pocock and Barlow initially listed two examples of this combination, subsequent verification has been lacking and the association has received much less notice than prolapse associated with second degree ASD. One of these five patients was clinically suspected of having mitral prolapse in addition to a patent ductus. In the other four patients, the echocardiogram provided initial evidence of the prolapse. The high incidence of congestive failure (80 per cent) and palpitations (60 per cent) in these patients could be explained by the presence of a large patent ductus alone.

Tetralogy of Fallot and congenital pulmonic stenosis are both congenital lesions without previously documented associated mitral valve prolapse. Five patients with repaired or palliated TOF were studied, and three (60 per cent) were found to have associated prolapse. Of the 15 patients with congenital pulmonic stenosis examined, five (33 per cent) had echocardiographic evidence of associated mitral valve prolapse. In neither of these conditions were physical findings typical of mitral valve prolapse found (possibly

because the primary lesion obscured them) and in neither were complications attributable to prolapse documented.

Two of our 14 patients with congenital left ventricular outflow obstruction had associated mitral valve prolapse. While to our knowledge this specific combination has not been previously noted, the association between LV outflow obstruction and other abnormalities of the mitral valve has been observed. Mitral regurgitation accompanying coarctation of the aorta is a recognized albeit uncommon association.[33] In one series of 53 hearts with coarctation of the aorta studied at autopsy 44 instances of associated mitral valve abnormalities were discovered.[34]

Neither of our two patients was thought to have prolapse before echocardiographic exam, and neither experienced complications or symptoms unexplainable by the outflow obstruction.

The two cases of Ebstein's anomaly with associated mitral valve prolapse (two of three cases of Ebstein's anomaly examined) found in this series supports previously reported evidence of the association between these two entities.[15]

The demonstration of mitral valve prolapse with four other miscellaneous congenital lesions (peripheral pulmonary artery stenosis, sinus of Valsalva aneurysm, tricuspid atresia, and idiopathic dilatation of the pulmonary artery) lends further credence to the widespread association between congenital heart disease and mitral valve prolapse.

b. Accuracy of echocardiography in the diagnosis of mitral valve prolapse. Prior to the widespread use of echocardiography the diagnosis of mitral valve prolapse relied on clinical impression (when the click-murmur complex was present) combined with left ventricular angiography. As echocardiographic techniques have become more widespread and refined, echocardiography has become the primary means of diagnosing prolapse. By 1971 a good correlation between echocardiographic and angiographic evidence of mitral valve prolapse had been demonstrated[19] and "typical echocardiographic patterns of prolapse were beginning to be elucidated.[21] Subsequent work by a variety of investigators refined echocardiographic techniques and criteria for diagnosing prolapse and established guidelines for minimizing false-positive diagnoses.[illegible] All patients in our series fulfill established echocardiographic criteria for mitral valve prolapse, and exhibit previously described patterns of valve motion typical of the syndrome.[illegible]

c. Etiology of mitral valve prolapse. Barlow and associates[1] believed that the click-murmur syndrome was a non-specific response to underlying abnormalities. They listed rheumatic heart disease, Marfan's syndrome, hereditary diathesis, and obstructive cardiomyopathy as underlying conditions capable of leading to mitral valve prolapse. Subsequent investigators have added coronary artery disease and abnormal left ventricular contraction to the list of possible etiologies. The demonstration that mitral valve prolapse is a common concomitant suggests that congenital heart disease must be added to the list of possible etiologies for prolapse. The unusually high incidence of mitral valve prolapse in a wide variety of congenital heart diseases compared to the lower incidence in presumably normal populations[illegible] suggests that congenital or constitutional abnormalities of the mitral valve, its supporting structure, or the left ventricle may be of major importance, rather than specific hemodynamic derangements, in the etiology of MVP.

d. Clinical relevance of the association between congenital heart disease and mitral valve prolapse. Since the use of echocardiography is well established for diagnosing and monitoring most forms of congenital heart disease, it is perhaps surprising that the prevalence of mitral valve prolapse has not attracted more attention. One possible explanation may involve the clinical masking of the physical findings of the mitral click and murmur by the abnormal auscultatory findings associated with each congenital lesion. In only three of our 40 cases was mitral valve prolapse considered clinically prior to echocardiography. Only two patients had the typical click-murmur on physical examination.

Historical data also failed to predict the presence of mitral valve prolapse associated with congenital heart disease. Although seven of the 40 patients experienced chest pain and 14 had experienced palpitations, it was frequently difficult to pinpoint the origin of these complaints, and they did not appear to be associated specifically with prolapse, or to be unusually frequent in this subgroup.

The present series is too small to judge the prevalence of known but infrequent complica-

tions of mitral valve prolapse such as SBE, arrhythmias, and sudden death when prolapse is associated with congenital heart disease. The case histories of the 40 patients point out several difficulties in the interpretation of data in the combined lesions. The possibility of SBE was actively considered in three cases. Although organisms were not isolated in any instance all three cases occurred in congenital lesions which, by themselves might be regarded as higher risks for SBE (two VSD one ruptured sinus of Valsalva). Although ECG abnormalities were frequently recorded, in most instances they were readily explained by the congenital lesion alone.

Conclusions

Our experience with 120 adults with congenital heart disease studied echocardiographically over the past three years suggests that associated mitral valve prolapse is much more common than previously recognized. Moreover prolapsing mitral valve seems to be relatively common in a wide variety of congenital heart diseases rather than being confined to a few lesions, as the recent literature appears to indicate. Since the clinical diagnosis of mitral valve prolapse may be particularly difficult when it occurs with congenital heart disease, a careful echocardiographic examination of the mitral valve in patients with congenital heart disease is essential. The effect of [illegible] prolapse on the prognosis of congenital [illegible] disease is unknown and awaits follow up of patients in whom the syndrome has been recognized.

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Creatine kinase isoenzyme MB (CK MB) in acute coronary ischemia

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CK MB has been found to be a very sensitive and specific indicator of acute myocardial infarction (AMI) Although the occurrence of CK MB has been reported in cases other than AMI such as muscular dystrophy dermatomyositis, hypothermia, and others, these disorders are not included in the differential diagnosis of AMI and therefore are of little importance in this clinical context. Moreover it has been stated that an elevated level of CK MB appears to differentiate myocardial necrosis from reversible myocardial ischemia. We wish to report five cases in which elevated levels of CK MB were observed in patients with acute coronary ischemia in whom no evidence was found for cardiac necrosis.

Patients and methods

Five patients with acute coronary ischemia presented below were examined for the presence of serum CK MB and myoglobin Blood samples were drawn every 2 hours following the onset of chest pain for 24 hours. Total serum CK determinations were performed according to the method of Rosalki (normal values up t 12 I U) For the detection of the CK MB fraction electrophoresis on cellulose acetate plates titan 3-iso (Helena Laboratories, Beaumont, Texas, U.S.A.) used. For the quantification of CK MB a d tometric method was employed by scanning electrophoretic fraction of MB with the "Q Scan Flurvis" of the same company The amo of CK MB was calculated as a percentage of total CK activity Significantly elevated CK in our laboratory is above 4 per cent of total activity Serum myoglobin levels were det mined by radioimmunoassay (myoglo RIA—Nuclear Medical Systems, Newport Bea California U.S.A.) The normal range of value 6 to 86 ng./ml. In our laboratory serum myogl bin levels in documented cases of AMI between 200 and 1,000 ng./ml.

Case reports (Table I)

Case 1 A 58-year-old man with a history of unstable angina was admitted to our coronary care unit (CCU) with acute chest pain of 1½ hours duration at which time anterior wall ST depressions were observed on the ECG Pain subsided on treatment with morphine No evidence of AMI was noted. During the second day of hospitalization acute chest pain developed with ST depressions as above. Pain was relieved with opiates and ceased after 20 minutes The ECG returned to normal also. Blood samples were then drawn every 2 hours as described above CK MB was found to be elevated 4 hours following onset of chest pain (7 per cent of total CK activity), reached a peak at 8 hours (8 per cent) and was undetectable 12 hours after the onset of pain Total CK ranged between 4 and 7

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Table I*

Case no.	Diagnosis	Range of total CK (I.U.)	Peak CK MB	Myoglobin range (ng./ml.)	Appearance time of MB (hours)	Time to achieve peak (hours)	Disappearance time (hours)
1	Unstable angina	4-7	8%	20-40	4	8	12
2	Unstable angina	9-13	9%	30-41	4	8	10
3	Unstable angina + old MI	5-13	17%	15-38	4	8	14
4	Acute coronary ischemia + intermittent LBBB	4-12	13%	24-32	4	8	12
5	Crescendo angina and stress-induced LBBB	8-11	12%	30-40	6	8	10

*All times relate to the onset of chest pains.

I.U. Myoglobin ranged between 20 and 40 ng./ml. The patient was discharged under massive propranolol treatment and isosorbide dinitrate. Two weeks later this patient was readmitted under the same circumstances and blood samples were drawn immediately following admission (2 hours following onset of chest pains). CK MB peaked 6 hours following the onset of chest pains (12 per cent) and was not detected at 12 hours. Myoglobin was in the range of 20 to 36 ng./ml. and total CK ranged between 7 and 12 I.U. This patient was referred for coronary angiography and surgery. During this period the ECG remained normal between bouts of pain.

Case 2. A 62 year-old man with effort angina of 6 years duration was admitted with chest pains at rest of over ½ hour duration. ST depressions were noted on the anterior wall leads of the ECG. Pain was relieved with opiates and the ECG returned to normal configuration. No evidence of AMI was noted. Blood samples were drawn as described above and elevated CK MB was noted 4 hours following onset of chest pain (6 per cent) and peaked 8 hours following the onset of pain (9 per cent). Total serum CK was 9 to 13 I.U. and the serum myoglobin was 30 to 41 ng./ml. The patient was referred for surgery. At no time was there electrocardiographic evidence of necrosis, nor were elevated levels of CK or myoglobin observed.

Case 3. A 68-year-old man with a history of inferior wall MI one year previously was admitted due to acute chest pains following diagnosis of unstable angina of 2 weeks duration. On admission anterolateral wall ST depressions were noted and Q waves on the diaphragmatic wall leads. During hospitalization he developed acute chest pain with ECG signs as above. Serial blood samples were taken as described and elevated levels of CK MB were noted 4 hours following the onset of chest pain (9.5 per cent) peaked at 8 hours (17 per cent), and disappeared 14 hours following the onset of this episode. Total CK was 5 to 13 I.U. and serum myoglobin was 15 to 38 ng./ml. At no time was infarction noted on the ECG apart from the old diaphragmatic wall infarction. This patient was also referred for surgery.

Case 4. A 73-year-old woman was admitted with acute chest pain. There was no history of coronary artery disease. The chest pain was of 1 hour duration during which time complete left bundle branch block (LBBB) appeared. Cessation of pain following isosorbide dinitrate administration was followed by the disappearance of the LBBB. After this no evidence of infarction was noted on the ECG. Serial blood samples were drawn and CK MB was found to be elevated 4 hours following the onset of pains (10 per cent) and peaked at 8 hours (13 per cent). CK MB was not detected in samples drawn later than 12 hours after the onset of pains. Serum myoglobin was 24 to 32 ng./ml. and total CK was in the range 4 to 12 I.U. This patient is under conservative treatment with propranolol.

Case 5. A 42 year-old woman with effort angina of 3 years duration which intensified 1 month prior to admission underwent ergometric stress testing. At 50 Watts the patient developed LBBB with severe retrosternal pain. The pain was of 20 minutes duration until it was relieved by sublingual nitrates. The LBBB disappeared 30 minutes

following testing. The patient was hospitalized and blood samples were drawn as described. CK MB was found to be elevated 6 hours following the onset of pain (10 per cent) peaked at 8 hours (12 per cent) and was undetectable at 10 hours. Total CK was in the range 8 to 11 I U and serum myoglobin was 30 to 40 ng./ml Following the disappearance of the LBBB pattern the ECG remained normal.

Discussion

CK MB is a highly sensitive indicator of AMI. Therefore it is of importance to determine whether CK MB may be elevated in circumstances which may be clinically confused with AMI We have described above five patients with definite evidence of acute coronary ischemia determined clinically and electrocardiographically At no time was there any evidence of myocardial infarction having occurred. Moreover in a follow up period of 4 months in our outpatient clinic, none of these patients showed evidence of infarction. In addition the occurrence of myocardial necrosis was excluded by the finding of normal serum myoglobin Myoglobin has been found to be an extremely sensitive indicator of myocardial necrosis. Thus the finding of normal serum myoglobin provides strong supportive evidence the exclusion of infarction however small in our patients. However our patients had significantly elevated values of CK MB albeit they had normal serum values of total CK.

Elevated CK MB was noted 4 to 6 hours following the onset of chest pain and disappeared completely 10 to 14 hours following the onset of pains. This may be contrasted with the time activity behavior of CK MB in myocardial infarction where CK MB peaks after 18 to 24 hours and remains detectable for a much longer period. We are thus forced to conclude that elevated values of CK MB may be found in some cases of acute coronary ischemia

Elevated levels of CK MB in acute coronary ischemia have been reported previously Elevated CK MB in the presence of normal serum total CK has also been found in patients with prolonged atrial tachyarrhythmias This may be related to ischemia since elevated values of coronary sinus CK activity have been reported in pacing induced ischemia In evaluating myocardial damage during coronary art ry gr fting in 60 patients, two patients were not d n whom there was marked cumulative CK MB activ[illegible] but normal serum levels of total CK a[illegible] unchanged electrocardiograms. All previous [illegible] ports of elevated CK MB in patients with isch[illegible] mia but without AMI have concerned only [illegible] small number of patients from much larger serie[illegible] Nevertheless those recurrent reports cannot [illegible] ignored Some of these patients could be postu[illegible] as having minor necrosis or subendocardia[illegible] infarctions, undetectable by conventional labora[illegible] tory techniques. Of particular interest, therefore is the report of six patients with elevated levels o[illegible] CK MB, no electrocardiographic changes, an[illegible] negative technetium 99m pyrophosphate scans. In the same report there was an additional patient with ischemic ST T wave changes, elevated CK MB and a negative scan.

For clinical purposes serum myoglobin assay may be utilized in place of technetium 99m pyrophosphate scanning for the detection of small areas of necrosis or the exclusion thereof Our findings corroborate those of a previous methodical search for patients with myocardial ischemia and elevated levels of CK MB. It seems highly probable that the presence of CK MB in acute coronary ischemia may be detected with greater frequency if serial determinations are made at short time intervals begining after a short period following the onset of chest pains.

W wish to acknowledge the kind assistance of Mr. J. [illegible] of Nuclear Medical Systems, Newport Beach, California, for the supply of myoglobin RIA kits.

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The reliability of coronary angiogram interpretation An angiographic–pathologic correlation with a comparison of radiographic views

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Coronary angiography has been accepted as a reliable method for the demonstration of the presence and extent of coronary artery disease. Previous studies correlating premortem angiographic interpretations with pathologic findings have demonstrated an 80 to 93 per cent agreement with more errors of underestimation of angiographic lesions than overestimation, although nonuniformity in definition of noteworthy lesions makes comparability of studies difficult.

It has been suggested that one of the reasons for discrepancies is related to postmortem alteration of the vessels. The tissue shrinkage occurring secondary to formalin fixation could lead to overestimation of a pathologic lesion. The angiographic interpretation of the same lesion would appear then, to be an underestimation. In the literature, a total of 119 patients[2] have had selective cine coronary angiograms (including 10 with a combination of cineangiograms and biplane angiography) which were correlated with pathological data. Of these 119 patients, only 70 have had postmortem coronary angiograms performed to aid in pathological examinations

In interpreting coronary angiograms it is usual practice to use several radiographic views to assess a lesion. It is also common to interpret as significant a lesion observed in one view only. This study was designed to evaluate the accuracy of single versus a combination of radiographic views by correlating premortem coronary angiograms with pathological data examined in the fresh, unfixed state and including the use of postmortem coronary angiograms.

Materials and methods

The study population consisted of 20 [illegible] patients who died an average of 57 days (range 1 to 194 days) following selective coronary angiograms performed for diagnostic evaluation [illegible] years 1970 to 1976. The etiologies of heart dis[illegible], pathologic data, and causes of death for [illegible] patient are shown in Table I.

Selective coronary angiograms were perfor[illegible] in multiple right anterior oblique and left ant[illegible] oblique projections by one of two technique[illegible] described previously by Sones and Shirey[illegible] an[illegible] Judkins and were filmed at 30 frames per sec[illegible] on 35 mm. Kodak film using a Picker cinefluo[illegible]graphic unit with a nine-inch cesium iodide int[illegible]ensifier image tube. All patients received subling[illegible] nitroglycerin prior to selective injection [illegible] minimize coronary artery spasm.

Pathologic studies were performed on [illegible] hearts in a fresh, unfixed state within 24 hou[illegible] following death. The coronary arteries we[illegible] injected with a barium sulfate mixture accordi[illegible] to the Schlesinger technique,[11] maintaining [illegible] injection pressure of 100 to 125 mm. Hg for [illegible] least five minutes. The vessels were longitudina[illegible]

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Table I Clinical and pathologic data

Pt.	Diagnosis	*Pathological data*				Cause of death
		Number of lesions		*Normal segments*	*Number of arteries with significant lesions*	
		*Significant**	*Insignificant*			
1	CAD	5	2	8	2	Probable AMI
2	AS, AI	0	2	12	0	Postoperative complications
3	AS, AI, CAD	2	12	5	1	Operative
4	AS	0	7	9	0	Sudden, due to aortic stenosis
5	CAD	4	11	4	2	Probable AMI
6	CAD	3	5	5	2	AMI
7	CAD	6	5	4	3	AMI
8	AS, AI	0	0	13	0	Operative
9	MR	0	3	12	0	Operative
10	CAD, VA	1	8	5	1	Refractory arrhythmia
11	CAD	4	10	10	1	Probable AMI
12	CAD	5	13	13	2	Aortic dissection, AMI
13	CAD	4	2	2	3	AMI
14	CAD	7	3	3	3	Probable AMI
15	CAD	4	10	10	3	Probable AMI
16	CAD	4	6	6	2	Operative
17	AS, CAD	4	11	11	3	Operative
18	CAD	4	4	4	3†	Probable AMI
19	CAD	7	1	1	3	Operative
20	CAD, VA	8	2	2	2	Operative
Total		70	121	121	35	

Abbreviations: CAD = coronary artery disease; AS = aortic stenosis; AI = aortic insufficiency; MR = mitral regurgitation; VA = ventricular aneurysm; AMI = acute myocardial infarction.
*See text.
†Patient No. 18 had only one view of the right coronary artery and at postmortem exam had total occlusion of the vessel. It was not included in this analysis.

ly dissected using the postmortem coronary angiogram (Fig. 1) to indicate the location of the lesion. The degree of obstruction was carefully noted by observation of the arterial lumen and by the degree of narrowing of the barium gelatin cast. The per cent reduction of the cross-sectional area of the vessel was determined for all observed lesions. All pathologic studies were performed by a single investigator who was a cardiologist experienced in cardiac pathology.[13-16]

Premortem coronary angiograms were reviewed on a Tagarno projector and interpreted by three cardiologists who recorded their interpretations *independently* on standardized forms dividing the coronary arteries into 15 segments. Readings of each segment in each vessel were made and *recorded separately* for each of the two views—right anterior oblique and left anterior oblique (Fig. 2). Angiographic lesions were read as per cent reduction in lumen diameter of the vessel. An average of the three independent readings was taken as the final interpretation. In each segment of the coronary arteries, each lesion was considered one luminal area for angiographic and pathologic correlation. Therefore, because of multiple lesions in several segments, the number of comparable luminal areas in those segments was greater than one in many instances. A normal segment or a segment with only one lesion was considered one luminal area for comparison.

Each pathologic and angiographic luminal area was classified as hemodynamically significant or hemodynamically insignificant. A significant angiographic lesion was defined as a 50 per cent greater reduction in the lumen diameter of the vessel. Since a 50 per cent reduction in lumen diameter results in a 75 per cent reduction in cross-sectional area, an *equivalent* significant pathologic lesion was defined as a 75 per cent or greater reduction in the cross-sectional area of the vessel. Insignificant lesions were those interpreted as less than 50 per cent angiographically or less than 75 per cent pathologically.

An average of the three readings of the left

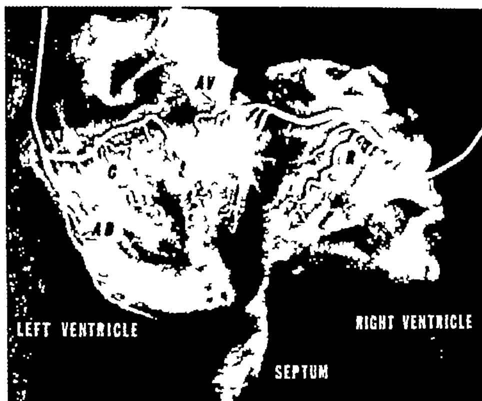


Fig. 1 Postmortem coronary angiogram of the fresh, unfixed postmortem specimen used for performance of dissection. AD = left anterior descending artery; AV = AV nodal artery; C = left circumflex artery; R = right coronary artery

anterior oblique and right anterior oblique views was compared to pathological data to determine whether a specific luminal area was considered significant or insignificant in *one* or *both* views of all cases where two views of the same segment were available. A combined view as defined in this paper requires that the definition of a significant or insignificant lesion for a specific luminal area be met on *both* left anterior oblique and right anterior oblique views.

Angiographic and pathologic interpretations of each luminal area were compared and categorized as follows. True positive areas were those interpreted as significant both angiographically and pathologically. True negative areas were those interpreted as insignificant or normal both angiographically and pathologically. False positive areas were those interpreted as significant angiographic areas but insignificant pathologic areas. False negative areas were those interpreted as insignificant or normal angiographic areas but significant pathologic areas. Results are further expressed as: Sensitivity defined as the number of true positives divided by true positives plus false negative—a measure of false negative, and specificity defined as the number of true negatives divided by true negatives plus false positive—a measure of false positive.

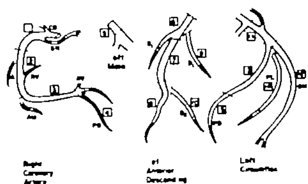
In every case of discrepancy between the angiographic and pathologic interpretations, the formalin-preserved pathologic specimen was reviewed. As a result of this, no changes were made.

Only two of the 20 patients had a dominant left coronary artery anatomic pattern, and therefore segment 15, the posterior descending from the circumflex, was not included in the results.

Results

There were 313 luminal areas in the left anterior oblique view and 311 luminal areas in the right anterior oblique view for analysis. Comparable luminal areas for both the left anterior oblique and right anterior oblique views were available in 301 instances.

The results of analysis for the right coronary artery system are illustrated in Fig. 3, the left anterior descending coronary artery system in Fig. 4 and the left main and circumflex marginal artery system in Fig. 5. Each major column



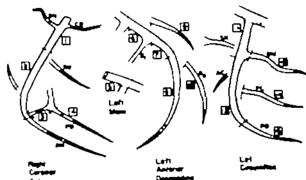


Fig 2. Schematic diagrams of the coronary artery segments in each radiographic view

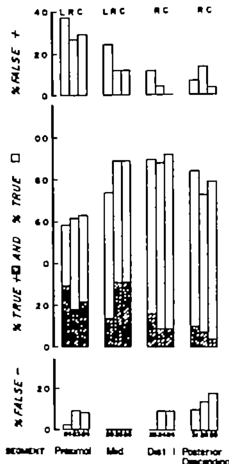


Fig. 3. An analysis of the right coronary artery system is shown for each radiographic view The left anterior oblique (L), right anterior oblique (R), and combined view (C) are illustrated. The number of luminal areas evaluated for each radiographic view and coronary artery segment is indicated at the bottom of each column. The percentage by radiographic view of true positive, true negative, false positive, and false negative readings for each segment of the right coronary artery system is shown *by the relative heights of the bars*

within the figures contains three columns each of which relates to specific radiographic views (L = left anterior oblique R = right anterior oblique and C = combined views)

The problem of false positive (overestimation) can be appreciated by attention to the top section, the problem of false negative (underestimation) by attention to the bottom section of Figs. 3, 4 and 5 An evaluation of accuracy for each segment and for each view can be appreciated by attention to the middle section of Figs. 3, 4, and 5.

A substantial number of false positive lesions are seen in the right, left main, and circumflex marginal systems using either single or combined views. The left anterior descending artery system is relatively free of false positive interpretations.

False negative interpretations are primarily a problem in the posterior descending, proximal left anterior descending, first diagonal, circumflex (proximal and distal) and obtuse marginal coronary arteries.

A summary of the angiographic analysis as it relates to single or combined views is shown in Fig. 6. Sensitivity and specificity for the left anterior oblique views were 72 per cent and 85 per cent, the right anterior oblique views were 78 per cent and 87 per cent, and combined views were 61 per cent and 93 per cent, respectively Hence, sensitivity is lower for the combined views, but specificity is higher

Discussion

Coronary angiographic interpretation in the majority of instances leads to correct analysis of the underlying coronary artery disease. However

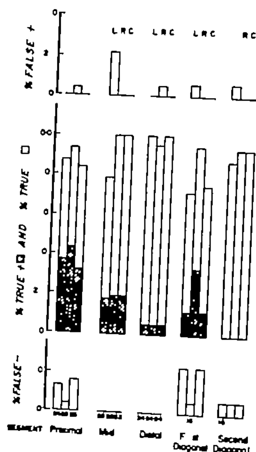


Fig. 4. An analysis of the left anterior descending coronary artery system is shown for each radiographic view. The left anterior oblique *(L)*, right anterior oblique *(R)*, and combined view *(C)* are illustrated. The number of luminal areas evaluated for each radiographic view and coronary artery segment is indicated *at the bottom of each column*. The percentage by radiographic view of true positive, true negative, false positive, and false negative readings for each segment of the left anterior descending coronary artery system is shown *by the relative heights of the bars*.

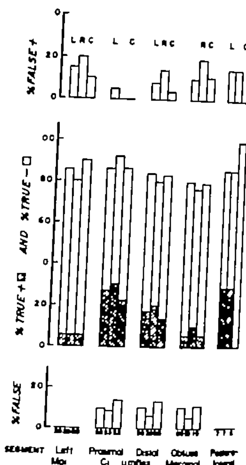


Fig. 5. An analysis of the left main and circumflex coronary artery systems is shown for each radiographic view. The left anterior oblique *(L)*, the right anterior oblique *(R)*, and combined view *(C)* are illustrated. The number of luminal areas evaluated for each radiographic view and coronary artery segment is indicated *at the bottom of each column*. The percentage by radiographic views of true positive, true negative, false positive, and false negative readings for each segment of the left main and circumflex coronary artery systems is shown *by the relative heights of the bars*.

it is common practice to use one view to determine the "significance" of a given lesion although if a significant lesion is observed in both the left anterior oblique and right anterior oblique views, reliability is thought to be increased. Our result of a 93 per cent specificity confirms the reliability of a lesion when observed in both views. Our results also suggest the best view for the left anterior descending coronary artery system is the right anterior oblique view having a sensitivity of 88 per cent with a specificity of 98 per cent and far exceeds that of the left anterior oblique or combined views.

The problem of false positives is most noticeable in the proximal segments of the right coronary artery system but is present to a lesser extent in all segments in at least one radiographic view. The reason for the false positive interpretation is unknown, but in some cases probably represents catheter induced spasm despite the routine use of nitroglycerin prior to coronary artery injection of contrast medium. Of the 16 luminal areas regarded as false positives in the proximal segment of the right coronary artery system using combined views, seven were associated with a normal coronary artery segment and nine were associated with definite but insignificant obstructive coronary atherosclerotic areas. Of the two luminal areas which were considered false positive in the left main coronary artery system using combined views, one had a 50 per cent pathologic lesion (insignificant), and the

other was normal. However the latter patient had a total 100 per cent proximal circumflex and an 80 per cent proximal left anterior descending coronary artery lesion. Hence, the presence of underlying disease may contribute to spasm of the proximal segments of arteries in the problem of false positives, but it does not account entirely for this phenomenon.

Because of the importance of detecting left main coronary artery disease, the problem of false positive interpretation of a significant lesion in this portion of the coronary artery is of particular interest. This problem was also recorded in a recent paper by Hutchins and associates, in which 71 per cent had overestimation of the left main coronary artery compared to 10 per cent in our series using combined views. This problem was of greater magnitude for single views in our study. The most prudent policy would be to require a significant lesion of the left main coronary artery to be present in both views. The use of special radiographic views,[14, 15] now commonly employed, may be solving this problem, although this should be substantiated by proper studies.

It is understandable why false negatives would be found in the proximal left anterior descending coronary artery in the left anterior oblique view since it is recognized that this is a poor view in which to assess that segment. Overlapping of the first diagonal on the left anterior descending coronary artery probably accounts for these false negative readings in the majority of cases in this artery and has been noted previously. The problem of false negative interpretation in the remaining arteries is of low incidence yet is a troublesome problem.

Coronary angiogram interpretation is thought to result in underestimation (false negatives) more often than overestimation (false positive). Our results (Fig. 6) substantiate this conclusion only if one requires a specific lesion to be present in at least two views. If one requires a lesion to be visible in only one view the number of overestimations (false positives) exceed those of underestimations (false negatives). This problem must be considered when interpreting coronary angiograms.

Our accuracy of combined views is 86 per cent when expressed as the sum of true positives plus true negatives, and it compares to that previously reported. Furthermore, when using both views, underestimation is the most frequent error as

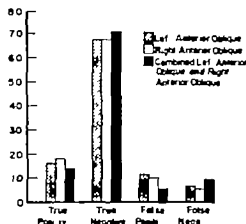


Fig. 6. Summary of results of angiographic analyses as it relates to either single or combined radiographic views.

noted above. These results suggest that the method of tissue preparation is not a major influence in the outcome of studies of this type.

Our results suggest the acceptance of a significant lesion in one radiographic view is associated with a noteworthy number of false positive interpretations, particularly in the proximal arteries. This can be solved in part by requiring a significant lesion to be present in both views, however this is accomplished with less sensitivity. Consideration should be given to less frequent routine use of the left anterior oblique view with more emphasis on the right anterior oblique view in several planes of rotation and obtaining hemiaxial views with the patient in the left anterior oblique view for filming the left coronary artery. Routine cusp injections initially may be helpful in the problem of false positives of the right proximal coronary artery. Further correlative studies of angiographic and pathologic areas will be necessary to substantiate these suggestions. One must accept a certain per cent of false positive and false negative interpretations in reading coronary angiograms. This is common to all other employed diagnostic tests, including the chest x ray[20] and electrocardiogram,[21, 22] as the informed interpreter is aware.

Summary

This prospective study correlates premortem coronary angiographic interpretation with pathologic findings including the use of postmortem

coronary angiograms. The reliability of a single radiographic view left anterior oblique or right anterior oblique, or combined views (left anterior oblique plus right anterior oblique) was examined. The most reliable interpretation, the combined view has a specificity of 93 per cent, but sensitivity is less at 61 per cent. Using a single view enhances diagnosis (sensitivity) but it leads to overestimation more frequently (decreased specificity) Proximal segments of the coronary arteries are prone to a significant per cent of false positive readings. The most accurate assessment of the anterior descending coronary artery system occurs with the use of the right anterior oblique with multiple views. Less routine use of the left anterior oblique view with increased use of the hemiaxial view is suggested for the angiography of the left coronary artery Initial cusp injections of the right coronary artery may avoid a high per cent of false positive readings in the proximal segment.

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Left ventricular performance during and after sickle cell crisis

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Although it is generally recognized that chronic anemia produces a high output state associated with cardiac hypertrophy, the influence on the myocardium may be affected by the specific form of anemia. Cor pulmonale secondary to pulmonary hypertension is well recognized in sickle cell anemia. In addition, left heart failure is known to occur in subjects in the third and fourth decades without the usual cardiac risk factors or valvular disease.

Defective hemoglobin synthesis in patients with sickle cell (SS) hemoglobin is not known to be paralleled by an analogous abnormality of cardiac contractile protein as a basis for heart failure. Microvascular occlusion by sickled red cells in the myocardium has been postulated to produce ischemic necrosis, which on a chronic basis may be the cause of cardiac decompensation. As an alternative hypothesis there has been indication that the many years of chronic hemolysis[1] in SS patients may result in deposition of iron in body tissues. This process is evidently less severe than in secondary hemochromatosis where a large iron load from multiple blood transfusions may lead to heart failure in the first or second decades.

To examine whether a milder form of left ventricular dysfunction may exist in patients with SS hemoglobin without the conditions for secondary hemochromatosis, subjects were studied noninvasively by the systolic time interval method supplemented by echocardiographic measurements. The question of ischemic injury was considered by serial testing of patients during and after an acute crisis as well as analysis of serum enzymes known to reflect cardiac injury. A time-dependent effect of the chronic hemolytic process as a potential basis for myocardial abnormalities was evaluated in different age groups.

Materials and methods

Eleven black patients admitted in sickle cell crisis were studied serially; four were restudied during a subsequent crisis. All subjects had hemoglobin SS by electrophoresis. For studies after crisis or at intercrisis intervals, additional subjects without recent illness were included at 1 to 5 months after their last episode. Patients were excluded if they were hypertensive, diabetic, obese, uremic, had known pulmonary disease, or were heavy smokers or addicts. Excessive use of ethanol or habitual drug usage was excluded by history and generally confirmed by a relative or close friend. Subjects with prior blood transfusions or oral iron medication were not included.

Diagnosis was based upon a presentation with pain in joints or skeleton that was usually similar to the symptomatology of prior crises, and was mild and moderate in degree. Most had a Grade 2 to 3 systolic murmur at the apex or left sternal border. Body temperatures per rectum during the first day were elevated by 0.6 to 1.7 F and usually returned to normal by day six. Serum electrolytes, glucose, and BUN were in the

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Table I Clinical data in sickle cell patients during crisis

Group SS	Age/sex	Hematocrit	Blood pressure (mm. Hg)	Duration of symptoms (hrs)	Cardio-thoracic ratio
L. W	13 F	28	120/80	4	0.46
L. L.	17 F	24	118/78	11	0.54
C. P	20 F	26	125/`5	5	0.48
K. M.	21 M	25	140/80	16	0.53
C. W	22 M	`0	128/74	17	0.49
D. W	22 F	31	130/90	17	0.47
P. M.	23 F	27	140/90	15	0.54
G. D	24 M	25	120/70	14	0.55
R. C.	26 M	31	126/80	20	0.50
L. S.	31 M	28	130/`6	20	0.53
R. B.	38 F	23	130/82	30	0.55
Mean		25	128/80	15	0.51
S.E.		1.3	2.2 1 7	2.2	0.01

Table II Left ventricular systolic time inter

	During crisis		Post-cris
	Heart rate	PEP/LVET	Heart rate
L. W	106	.332	77
L. L.	93	.367	96
C. P	83	.361	90
K. M.	89	.262	84
C. W	100	.303	73
D. W	64	.325	114
P. M.	104	.502	99
G. D.	107	.488	81
R. C.	76	.321	69
L. S.	77	.433	77
R. B.	97	.299	106
Mean	91	.363	88
±	4.3	.024	4.3
Normals (N = 22)	67	.313	
±	1.6	.006	
P vs normals	< 0.0001	< 0.05	< 0.0001

*None of values differed significantly from post-crisis.

normal range. Hematocrit, blood pressure, and heart rate are indicated in Tables I and II.

Twelve-lead ECG s and chest roentgenograms were obtained at the time of admission and were repeated within three days. Serum samples were analyzed for SGOT (upper limit 40 units) and CPK (upper limit 145) Serum samples in some of the patients were kept at 0° C and analyzed for identification of the isoenzymes of CPK.

Systolic time intervals were measured within 24 hours of admission to the hospital, generally before medications were administered. This set of studies was repeated after 3 to 5 days and again after 7 to 10 days when the crisis had subsided and medication had been discontinued.

The systolic time intervals were measured as described by Weissler and associates[16] from simultaneous ECG phonocardiogram, and carotid pulse tracings. Recordings were done on an oscillographic recorder (Electronics for Medicine, White Plains, N Y) at a paper speed of 150 mm./sec. and time lines at 0.02 sec intervals. Ten to 12 complexes were analyzed and averaged. Preejection period (PEP), left ventricular ejection time (LVET) and electromechanical systole (QS²) were calculated and then corrected for heart rate, using Weissler s regression equation

Twenty two volunteers without heart disease or anemia with a mean age of 34 ± 1.9 years, served as a control group. All studies were done between 8:00 A.M. and 12:00 noon in the postabsorptive phase and supine position In addition six anemic subjects without sickl cell disease within the age range of the SS group were stud to determine the effects of comparable degree chronic anemia without sickle disease on systolic time intervals. These subjects h chronic intermittent blood loss 3 to 17 months duration and had no cardiac risk factors.

To further evaluate left ventricular functi SS subjects had echocardiograms at interval intervals and were compared with normals similar age range. The echocardiograms we obtained with a Hoffrel Model 101 Ultrasc scope interfaced to an Electronics for Medici DR 12 amplifier recorder system, for measur ment of several left ventricular parameters

Results

During the period of crisis, precordial che pain was not present and there were no significan abnormalities of the ST segment or pathologic waves. The patients studied during crisis repre sented a relatively broad range in terms of ag and number of past crises. Hematocrits we moderately reduced to a mean of 25 ± 3 and th cardiothoracic ratio as judged from a chest roent genogram was enhanced in virtually all (Table I) The values for systolic time intervals measure on the first day of crisis are indicated in Table II Although heart rate was higher than in th normal group, there were no significant chang

Table III Serum enzymes

	SGOT		CPK Total		CPK MB isoenzyme (% of total)	
L. W	14	20†	98*	20†	4	1.0
L. L.			73	68		
C. P	25	64	110	33	1.8	3.9
K. M.	47	31				
E. W	31	25	39	27	2.7	1.4
D. W	25	24				
P. M.	30	27	31	34	2.9	2.1
G. D.	15	10	78	51	2.1	2.2
R. C.	37	32				
I. S.	35	36	26	27	0.3	0.7
R. B	–	–	45	42	2.4	1.9
Mean	28.8	29.8	62.5	39.0	1.94	1.88
±	3.5	3.9	11.2	6.0	.44	.40

*Blood samples obtained on admission to hospital before any injections.
†Samples obtained on day 3 or 4.

in the individual time intervals when corrected for heart rate (LVETI, PEPI, QS_2I). The ratio of PEP/LVET was significantly higher than normal in the initial study. In the 3 to 7 day period, the PEP/LVET ratio was higher than normal but not significantly different from the initial study at 0.385 ± 0.03. In the post-crisis period when the patients were afebrile, both PEPI and QS_2I were significantly abnormal. *The systolic time interval ratio was further elevated above normal to* 0.407 ± 0.02, although not significantly different from values of the initial day.

Four individuals were restudied during an additional crisis. Both the initial and post-crisis studies were significantly abnormal and did not differ significantly from each other. In these four subjects, the post-crisis ratio of PEP/LVET was 0.412 ± 0.24 compared to 0.390 ± 0.02 on the repeat study.

Serum enzymes were determined on the day of admission to determine if acute myocardial necrosis was present. SGOT was found to be within normal limits in the nine patients assayed and there was no significant change in the repeat analyses. Total CPK activity was slightly elevated on the day of admission and was substantially reduced by days 2 or 3. To determine the nature of the CPK elevation, isoenzyme activity was assessed in seven patients. In none was there a significant elevation of the MB

Table IV Age and intercrisis systolic time intervals

Name	*Age/sex*	*Hct*	*Crises*	*Heart rate*	*PEP/LVET*	*C/T*
Group A						
L. W†	13 F	25	16	77	.474	.46
A. T	13 M	32	1	62	.299	.45
Wa. W	14 F	27	4	76	.351	.46
L. L.†	17 F	24	15	107	.408	.54
W. B	18 M	25	2	75	.274	.56
C. P†	20 F	26	3	90	.312	.48
S. J	21 M	24	4	56	.263	
K. M.†	22 M	21	22	84	.293	.53
Mean	17.3	23.6	8.4	78.4	.336	.50
S.E. ±	1.28	1.12	2.84	5.63	.023	.02
Group B						
C. J	23 M	24	42	71	.377	.51
P. M.	23 F	26	27	90	.490	.53
G. B.	23 F	18	15	73	.375	.50
G. D.†	24 M	21	49	61	.414	.55
S. W	24 F	17	2	73	.335	.51
R. C.†	28 M	31	31	69	.455	.50
I. S.†	31 M	26	24	77	.539	.53
Wl. W	34 M	30	37	100	.459	
R. B.†	38 F	19	60	106	.405	.55
J. T	42 M	28	16	70	.379	.51
Mean	28.8	24.20	30.3	81.4	0.425	0.521
S.E.‡	2.23	1.63	5.48	4.1	0.021	0.006
P‡	.009	NS	.006	NS	.02	NS

*Group A patients were less than 23 years of age; Group B patients are at least 23 years old.
†Data were obtained no sooner than seven days after crisis. All others studied only at intercrisis. Each patient was normotensive.
‡Group A vs B is unpaired t test with equal variances.

isoenzyme, the MM fraction was elevated in several individuals and declined by days 3 and 4. Thus, no evidence of enzyme leakage from cardiac tissue was observed during the sickle cell crisis.

To determine whether a cumulative effect of the hemolytic process as judged by age may have been a determinant of the abnormal systolic time intervals, subjects studied after crisis and four additional individuals seen during an intercrisis period were assessed. Those in Group A were less than 23 years and those in Group B were at this age or older. As indicated in Table IV, PEP/LVET ratio in the younger group was not significantly different from normal controls. However in Group B the ratio was *significantly increased* at 0.413 ± 0.03. The hematocrit, heart rate and cardiothoracic ratio were at similar levels to those found in Group A but the cumulative number of crises were greater in Group B. The effect of age

Table V Chronic anemia without sickle cell disease

	Sex	Age	Hct	Hr	B P	QS₂Ix	PEPIx	LVETIx	PEP/LVET
J N	M	19	27	110	120/85	561	133	429	.364
C M.	F	25	24	75	115/75	549	132	416	.345
R. W	F	28	23	59	110/70	548	140	408	.388
B. W	F	34	26	61	115/76	531	125	407	.324
M. M.	M	38	20	75	120/80	532	115	417	.293
Mean		34.4	26 0	6	116/78	544	102	416	.330*
S E		8. 4	2.12	9 14	2.4/2.23	5.57	25.90	4 0	0.014

Unpaired t test
vs Normals (Table II) N.S.
Group A (Table IV) N.S
Group B (Table IV) P < .02

Table VI Intercrisis echocardiography

Patient	Age/Sex	LVID*	% F.S.	Vcf Circ./sec.	E.F	P.W.D.
Group A						
L W	13 F	5.0	33 0	1.217	.63	0.8
C. P	21 F	4.8	33.3	1.646	.70	0.7
S. J	31 F	5 0	36.9	1.221	8	0.8
C. W	22 M	5.9	37.3	1.519	75	0.9
K. M.	22 M	5.3	39 6	1 357	78	1.1
Mean	19.8	5 2	36 0	1.393	0.77	0.86
S.E. ±	1 7	0.2	1.3	0.085	0.021	0.06
Group B						
P M.	23 F	5 9	27.9	1.157	.64	0.7
C. J	23 F	6 2	27.0	.809	.61	0.8
S. W	24 F	5.3	40.6	1.175	77	0.9
D	25 M	4 9	28.5	1.306	.63	1.1
R. C	26 M	4.3	33.3	1.265	.69	0 8
I S	32 M	6.3	34.0	1.133	.62	1.3
W Wa.	34 M	5 0	34.0	1.514	71	
J. T	42 M	6 0	26 8	0 809	.60	9.8
Mean	28 6	5 5	31.5	1 173	.66	0.93
S E ±	2.4	0 26	1.7	0.060	0.021	0 08
Normals						
Mean (N = 8)	31	4 64	34.4	1.24	—	.96
S E ±	2	13	1 9	.06	.02	.03
P (normal vs Group A)		< 0 03	< 0 05	NS	NS	NS
P (normal vs Group B)		< 0 01	NS	NS	< 0.06	NS
Group A vs B		NS	< 0 06	< 0.09	< 0.005	NS

Abbreviations LVID = left ventricular end-diastolic internal diameter (in cm.), F.S = fiber shortening; E F = ejection fraction, P.W.D. = posterior wall thickness (in mm

may be largely dependent on the severity of the hemolytic process or on the number of crises, as suggested by the fact that the two subjects in Group A with PEP/LVET above .40 had at least 15 crises.

Since anemia per se is known to affect the cardiovascular system, five individuals were selected who had no known cardiac risk factors but who had evidence of chronic blood l[oss] Hematocrit levels had stabilized by the tim[e of] the study The levels of heart rate and arte[rial] pressure were comparable to the sickle [cell] patients. However the ratio of PEP/LVET [was] *not significantly different* from normal but [was] significantly less than in the Group B subj[ects] (Table V)

Echocardiographic studies in some of the inter crisis subjects of Groups A and B as well as additional sickle cell patients between crises also revealed a difference in left ventricular performance (Table VI). Group A parameters were similar to normals, except for a larger left ventricular end-diastolic internal diameter and greater per cent fiber shortening, presumably due to the chronic anemia. Group B despite a larger ventricular end-diastolic diameter had significantly reduced ejection fraction and a nonsignificant reduction of fiber shortening compared to normals. Ejection fraction was also diminished when compared with Group B.

Discussion

As a measure of left ventricular performance the systolic time interval method has been found to be sensitive and reliable, as well as reproducible in normals.[14] In this study of sickle cell patients determinations during two different crises indicated a reasonable degree of reproducibility. Systolic time intervals were sequentially determined during sickle cell crisis to assess whether there was evidence of abnormal myocardial function consistent with an acute ischemic process. The latter has been postulated to exist due to microthrombi formed by the aggregates of sickle blood cells. The observed patterns of the systolic time intervals during and following crisis contrasts with that occurring during myocardial infarction. Both situations are usually characterized by acute phase reactions for several days, which may in that period alter venous return, afterload, and neurohumoral regulation so as to affect the time intervals. During uncomplicated acute infarction, the abnormal ratio present on the first day appears to persist at about the same level through the first week.[13] By contrast, during crisis the ratio on the initial day was less abnormal than after the crisis, suggesting that myocardial ischemic injury was not present.

Supporting this view was the absence of cardiac symptoms and ECG changes consistent with acute ischemia. In addition the acute event was not associated with elevation of serum SGOT or CPK MB isoenzyme, although transient increments of MM, presumably from skeletal muscle, were observed. Since it is not yet known whether necrosis of a small quantity of myocardium can occur without release of detectable levels of CPK-MB into the serum, these findings only exclude ischemic injury of sizeable portions of heart muscle.

The observation that systolic time intervals were normal in anemic subjects without sickle cell disease is consistent with a prior study in which patients at this level of hematocrit reduction had time intervals within the normal range.[14] While it would appear that markedly reduced red cell mass can be associated with either substantially shortened or prolonged time intervals and heart failure, this degree of anemia was not present in our patients.

Abnormal left ventricular performance observed after crises or at intercrisis intervals was not observed in a prior study of sickle cell patients in which the temporal relation to acute crises or their relative number were not indicated.[14] Individuals less than 23 years of age had normal ventricular function by two noninvasive techniques, in agreement with our study. Older individuals consisted of seven females and four males. The mean PEP/LVET in the females was 0.32. While the series of males was too small to analyze statistically two were clearly abnormal at 0.42 and one was borderline at 0.35. In comparing the individuals over 23 years by sex in our own series, the males had a ratio of .446 ± .035 and females a ratio of .368 ± .023. Thus, the negative conclusion of the previous report may have been due to the relatively few males in the older group.

An additional factor may relate to the number of crises in each patient. Even in the young patients forming Group A, those with the more abnormal systolic time intervals had at least 15 crises, while those in Group B with only several such episodes tended to have normal time intervals. The general relationship of diminished ventricular function to age was supported by our echocardiographic studies, which indicated that only Group B subjects had a reduced ejection fraction, despite an enhanced left ventricular end-diastolic diameter.

Support for the view that the cumulative effect of chronic hemolysis and multiple crises over the years affect cardiac function is provided by reports on the occurrence of heart failure in patients with sickle cell anemia.[14] In the earlier study the two subjects who died of congestive heart failure with pulmonary edema were males, 30 and 32 years old. In the latter study congestive heart failure that was presumably left and right-sided occurred in three individuals between

ages 33 and 44 years. In both studies, increased interstitial fibrous tissue and edema were observed, with vacuolization of myocardial fibers in the left ventricle. Microscopic fibrosis has also been described in a prior report.[1]

The mechanism of the abnormal left ventricular performance in the older age group is not known. It is possible that the cumulative effects of anemia or arterial hypoxia on the process of hypertrophy may alter cardiac function in the long term process of sickle cell disease as compared to the lesser chronicity of the individuals with blood loss anemia. However the role of chronic hypoxia would appear unlikely in view of the reported normal left ventricular status in life long residents at high altitude.

Although classic hemochromatosis of the secondary type was not a factor in these patients, many years of chronic hemolysis are known to exist in patients with SS hemoglobin. Since serum ferritin concentrations are substantially elevated, significant deposition of iron in tissue may occur. In acquired iron storage disease of children who are recipients of many blood transfusions, left heart failure frequently appears by 20 years of age in contrast to at least a decade later in sickle cell anemia. Although a definitive morphologic study of myocardium is not available, the findings that interstitial fibrosis and ultimate loss of myocardial fibers that occurs in emochromatosis presumably as a reactive response to iron loading, may also be seen in patients with SS hemoglobin suggests that some patients who survive well into adulthood may incur some degree of left ventricular dysfunction on such a basis.

Summary

Although microvascular occlusion has been considered a basis for pathophysiology of the myocardium during the crisis of sickle cell anemia, the status of the left ventricle is uncertain. To determine if left ventricular performance is affected by crisis 11 patients were evaluated noninvasively by the systolic time interval method on the first day of crisis and serially until recovery. There were n significant differences in the time intervals over this period. In addition since the serum CPK MB isoenzyme was not elevated during crisis and evidence of acute injury was not present on ECG myocardial necrosis appeared unlikely. Four patients on subsequent admission exhibited systolic time interval values similar to the earlier crisis.

To determine if there were chronic changes in cardiac function, subjects with sickle cell hemoglobin were studied between crises. Those under 23 years of age were not dissimilar from a group of normals and a group of patients with chronic blood loss anemia. A significant abnormality of the PEP/LVET ratio was observed in subjects over 23 years of age. Similar observations were made on echocardiography with subjects over the age of 23 demonstrating an abnormal ejection fraction compared to the younger group, despite enhanced end-diastolic diameter. Thus, it is suggested that the chronic hemolytic process in subjects with sickle cell anemia may effect cumulative myocardial alterations, resulting in chronic cardiac malfunction in the apparent absence of acute ischemia during crises.

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Left ventricular function before and following surgical treatment of mitral valve disease

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Mitral stenosis was the first form of acquired heart disease to be successfully treated with surgical techniques when mitral commissurotomy was introduced in the 1940's. In the late 1950's, open heart procedures for the treatment of mitral regurgitation were developed, and mitral valve replacement became available in the early 1960's. Despite more than 25 years of experience with the surgical treatment of mitral valve disease and about 15 years of experience with mitral valve replacement, the changes in left ventricular function that occur following these procedures have not been fully defined.

This paper describes the function of the left before and one year following successful tral valve surgery Patients were selected who had received adequate reconstruction of the mitral valve or had a well functioning prosthesis. Special attention has been directed towards the changes in left ventricular volume, stroke volume, ejection fraction, and left ventricular mass which have resulted from surgical therapy in an effort to define the reversibility of left ventricular hypertrophy dilatation, and abnormal pump function in mitral valve disease

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Methods and patient material

Since the mid 1960's, many patients who have been treated with mitral valve surgery have undergone postoperative hemodynamic and angiocardiographic evaluation of the reconstructed or prosthetic valve. Nineteen patients operated upon between 1969 and 1974 have been selected from this group because they

1 Had a hemodynamically well functioning mitral valve at the time of postoperative study.

2. Had adequate left ventricular pressure and biplane angiocardiographic data from both the preoperative and postoperative studies to allow the construction of left ventricular pressure-volume diagrams to assess ventricular performance and hypertrophy

Nineteen patients with mitral valve disease without symptoms or electrocardiographic evidence of ischemic heart disease comprise the clinical material of this report. There were 15 men and four women this unusual ratio of men to women with mitral disease is because 15 of the patients are from the Seattle Veterans Administration Hospital. Seven patients had predominant mitral regurgitation (MR) defined as a calculated valve orifice greater than 2.5 cm. and more than 2.5 L./min./M of MR. Six patients had pure mitral stenosis (MS) with a valve orifice less than 1.4 and less than 1.0 L./min./M. of calculated regurgitation. Six patients had combined (MS-MR) defined as a valve area less than 2.5 cm. and more than 1.0 L./min./M. of calculated regurgitation. Patients with significant aortic valve disease were excluded. The patients' ages averaged 48 ± 9 years at the time of operation, and the postoperative cardiac catheteriza-

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Table I

	Age	*Mos. post surgery*	*CI L./min./M.*	*Δ AVO₂ ml. O₂/100 ml.*	*LV EDP*	*Mitral valve gradient (mm. Hg)*	*Mitral regurg. L./min./M*
			N = 6	N = 6	N = 6	N = 4	N = 4
MS							
Preop mean	45.9	11	2.7	57	8	17.3	0.2
± 1 Std Dev	±9.7	±9	0.5	10	10	9.4	0.3
Postop mean			2.7	51	3	6.7	0
± 1 Std Dev			0.7	14	10	4.3	0
p <			NS	NS	NS	NS	NS
			N = 5	N = 5	N = 6	N = 5	N = 6
MS + MR							
Preop mean	47	12	2.0	68	8	12.5	1.3
± 1 Std Dev	4.5	±10	0.3	6	5	8.8	0.7
Postop mean			2.8	55	9	7.4	0.4
± 1 Std Dev			0.7	12	4	2.1	0.5
p <			NS	NS	NS	NS	NS
			N = 7	N = 7	N = 7	N = 4	N = 5
MR							
Preop mean	48	8	2.4	63	17	3.7	3.6
± 1 Std Dev	8.2	±2	0.7	16	3	4.7	1.6
Postop			2.5	54	11	8.4	0.5
± 1 Std Dev			0.6	9	6	4.6	0.4
p <			NS	NS	0.05	NS	NS

Abbreviations: CI = cardiac index (Fick technique); Δ AVO₂ = arterial-venous oxygen difference, LVEDP = left ventricular end-diastolic pressure.

tion was carried out 11 ± 9 (mean ± 1 Standard deviation) months postoperatively. The surgical procedures included five mitral commissurotomies, three annuloplasties, and 11 valve replacements. The replacement valves included four homografts, two porcine heterografts, four Beall valves, and one Starr Edwards prosthesis.

Both pre- and postoperatively patients were studied by right, retrograde aortic, and transseptal catheterization. Prosthetic valve gradients were measured simultaneously between the left atrium and the left ventricle. Pressures were recorded through fluid filled catheters with Statham 23-DB, 23-GB or microdisplacement solid state transducers. Special efforts were made to achieve an air free system to produce a high frequency response as previously reported from this laboratory.

Cardiac output was measured by the direct Fick method immediately prior to angiography in close relationship to measurement of pressures in the left ventricle and aorta. Regurgitant volume (RV) was quantitated by comparison of the forward stroke volume determined by the direct Fick method and the angiographically determined stroke volume and expressed in liters per minute/M. Since patients with significant aortic regurgitation were excluded from this study the calculated regurgitation occurs at the mitral valve. Because of inherent error in both the quantitative angiographic method for measuring left ventricular stroke volume and the Fick technique for determining cardiac output, small volumes of MR were occasionally calculated at the time of postoperative evaluation (see Table I). Patients who had visualization of significant MR on postoperative angiography were excluded from this report.

Angiocardiography was carried out with the injection of 50 to 80 ml. of contrast material at a rate of 15 to 20 ml./sec. into the left atrium or left ventricle. Biplane anterior and left lateral angiographic examination was carried out at either 12 exposures per second and recorded with an Elema-Schonander roll film changer (15 cases) or at 60 frames per second on 35 mm. cine film (four cases).

A representative left ventricular pressure complex recorded at 100 mm./sec. paper speed just prior to left ventricular injection was digitized at 100 points per second with the aid of an x-y plotter. The angiograms were reviewed, and a

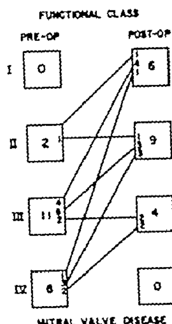


Fig. 1 This figure presents the NYHA Functional Class of each patient before and after mitral valve surgery

normally conducted well opacified cardiac cycle not preceded by a premature ventricular beat was selected for analysis. The longest length and area of the ventricle were determined on each biplane film pair and the left ventricular wall thickness was determined during end-diastole measured at the midportion of the free wall on the AP films. From this data, left ventricular volume and left ventricular mass were determined by methods previously described and pressure-volume loops were constructed. The ejection fraction (EF) or ratio of left ventricular stroke volume (SV) to left ventricular end-diastolic volume (EDV) is reported as a per cent Left ventricular mass (LVM) determined at end-diastole is also corrected for body surface area. Left ventricular systolic work (SW) was determined from the area enclosed by the pressure-volume loop and is expressed in gram meters per beat

Results

The clinical results of these patients following surgery are shown in Fig. 1 with 17 of the patients in Class III or IV preoperatively and 15 in Class I or II postoperatively The basic hemodynamic data are shown in Table I The cardiac index increased in patients with MS-MR and MR, but this change was not significant The arteriovenous oxygen difference (AVO) decreased in all subgroups but this change was also insignificant in all subgroups of patients. The left ventricular end-diastolic pressure (LVEDP) was elevated preoperatively in patients with MR and decreased from 17.3 ± 3 to 11 ± 6 mm. Hg ($p < .05$) following surgery The mitral valve gradient fell in patients with MS and MS-MR and increased in those with MR due to the additions of a small gradient across the prosthetic valves, but none of these changes were significant within the three subgroups.

The quantitative angiocardiographic data are presented in Table II. The mean heart rate during angiography was unchanged between the pre- and postoperative studies, although considerable variation was present. The EDV was unchanged before and after surgery in MS and MS-MR and fell significantly in those with MR from 124 ± [illegible] to 96 ± 35 ml. ($p < .01$) (see Fig. 2) while ES[illegible] did not change in any subgroup. The SV fell [illegible] MR patients from 67 ± 14 to 38 ± 11 [illegible] ($p < .01$) and remained unchanged in those with MS and MS-MR. The EF which was low normal preoperatively in MS and moderately low [illegible] MS-MR, did not change after surgery while [illegible] patients with MR it fell significantly from 55 ± 12 to 43 ± 15% ($p < .05$) following surgery as shown in Fig. 3. Four of the seven patients with MR had a greater than 10 per cent reduction [illegible] EF including the two patients with abnormal[illegible] low preoperative values, while the other th[illegible] patients had no change in EF after surgery N[illegible] that no patient with MR had an increase in [illegible] after surgery

LVM was increased in patient subgroups [illegible] regurgitation and showed no change follow[illegible] surgery despite a significant decrease in regurg[illegible] tion in both MS-MR and MR patients (Fig. [illegible] Systolic work had a tendency to increase [illegible] patients with MS and MS-MR and decrea[illegible] significantly in those with MR (see Table II)

Discussion

In 1970 we reported the quantitative angio[illegible] diographic findings in 100 patients with mi[illegible] valve disease who had undergone cardiac ca[illegible] terization and angiography prior to considera[illegible] of cardiac surgery In that report, there wer[illegible] patients with MS 35 patients with MS-MR, [illegible] 29 patients with MR. The methods used [illegible] determine left ventricular volumes and mass [illegible] nearly identical to those utilized in the pre[illegible] studies.

Comparison of preoperative values for E[illegible] RV EF and LVM has been made between t[illegible]

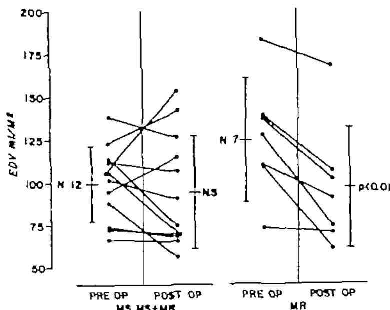


Fig. 2. This figure presents the end-diastolic volume in ml /M. (EDV ml/M.²) in patients with MS and MS-MR (*left panel*) and those with MR (*right panel*) before and after surgery. The EDV/M. was reduced significantly ($p < .01$) in patients with MR following mitral valve surgery.

Table II

		Angio HR	EDV/M	ESV/M.	SV/M	EF %	Mass/M.	SW gmM./beat
MS N = 6	Preop	71	86	43	43	51	106	86
	± 1 SD	19	19	17	11	12	23	22
	Postop	88	72	37	35	40	120	113
	± 1 Std Dev	19	19	16	6	11	25	47
	p <	NS	NS	NS	NS	NS	NS	NS
MS + MR N = 8	Preop	78	113	67	45	41	125	94
	± 1 SD	21	16	24	11	13	32	26
	Postop	74	116	66	60	44	140	112
	± 1 Std Dev	13	30	22	12	8	32	41
	p <	NS	NS	NS	NS	NS	NS	NS
MR N = 7	Preop	93	124	58	67	55	142	134
	± 1 SD	20	36	29	14	12	56	24
	Postop	86	96	57	38	43	143	97
	± 1 Std Dev	23	36	35	11	15	57	32
	p <	NS	0.01	NS	0.01	0.05	NS	0.01
Normal Group		76	71	26	45	63	93	106
N = 50	± 1 Std Dev	16	16	8	9	9	18	28

Abbreviations: EDV = left ventricular end-diastolic volume, ESV = left ventricular end-systolic volume, SV = stroke volume; EF = ejection fraction, Mass = left ventricular mass; SW = left ventricular stroke work.

patients who are the subject of this report and those described earlier. The subgroup with MS compares closely with our earlier experience. In patients with MS-MR, the EF is lower in the present series, 41 ± 13% versus 60 ± 10% and the RV is also less, 1.3 ± .7 versus 1.8 ± 1.1 L/min. In patients with MR, the EF is also lower in this series, 55 ± 12% versus 62 ± 12% and the RV is also less, 3.6 ± 1.6 versus 4.8 ± 2.6. The present series of patients, therefore, have less regurgita

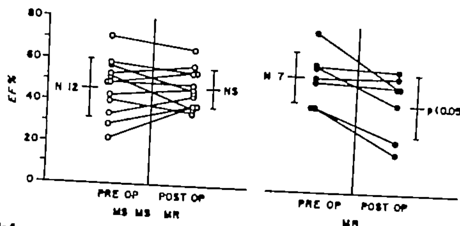


Fig. 3 This figure presents the jection fraction (EF %) in patients with MS, MS-MR (*left panel*), and those ... MR (*right panel*) before and after mitral valve surgery Note that a significant decrease was seen in EF in patient with MR following surgery

tion and more left ventricular dysfunction than those described earlier These differences probably relate to changes in patient population. The earlier series contained many young patients with severe MR who were studied in the early 1960's when the first successful mitral valve prosthesis became available. Such patients are now less frequently seen in our clinics and are usually operated upon earlier in the course of their disease. The relatively poor results reported here in MR patients may not be representative of all patients with MR It has been our clinical impression that patients with acute or subacute MR may have a more favorable postoperative course as well as some younger patients with chronic rheumatic MR. We have never however observed a patient with a low EF preoperatively who had a documented increase in EF after surgery

The results of this study indicate very little change in left ventricular size or function in patients following surgical correction of MS or MS-MR. Comparison of the results in these two subgroups shows few differences between them. This indicates that when reduction in the mitral valve orifice due to rheumatic valvular disease is less than 2.4 cm. the severity of regurgitation is not great and the resulting hemodynamic abnormality is dominated by the stenotic lesion. Symptomatic relief following valve surgery is, therefore, not usually related to changes in left ventricular function but due to lower left atrial and pulmonary venous pressures, with reduction in symptoms resulting from pulmonary enous congestion.

The results in patients with MR we[re] different from those in patients with M[S] MS-MR. Postoperatively there were sign[ificant] decreases in EDV and SV without a reduc[tion in] ESV which resulted in a reduction in EF fr[om ...] per cent to 43 per cent. This change can[not be] accounted for by a change in HR during ang[iogra]phy The range in HR before and after surg[ery in] the MR patients was 65 to 115. The gr[eatest] change in HR in a single patient was from [...] preoperatively to 78 following surgery [The] decrease in EF is probably due to an increa[se in] afterload which results from removal of the [low] resistance outflow from left ventricle to [left] atrium following mitral valve replacement.

Failure of regression of left ventricular hyp[er]trophy following surgical treatment of MR [is] unexpected because of the substantial reduct[ion] in LVM we have observed after aortic va[lve] replacement in patients with aortic regurgitati[on] (AR) Five patients with AR were stud[ied] 18 ± 9 months after surgery and those with M[R] were studied 6 ± 2 months postoperatively Th[e] five patients with AR had 3.9 ± 1.5 L/min/M of aortic regurgitation, while the seven patients with MR in this report had a similar volume of regurgitation of 3.6 ± 1.6 L/min/M. Because of the large pressure component of SW in those with AR, preoperative values for SW were higher in AR patients (210 ± 61 gmM) when compared to those with MR (134 ± 24 gmM). Following surgery SW was reduced to 125 ± 26 gmM ($p < .01$) in AR patients and to 97 ± 32 gmM ($p < .01$) in those with MR. The lesser reduction in SW and possibly the shorter follow up period

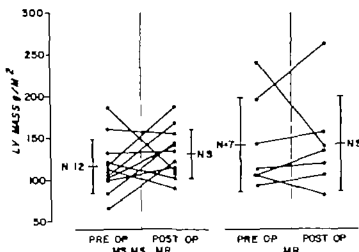


Fig. 4. This figure presents the left ventricular mass in gm./M. (LVMass gm./M.) in patients with MS, MS-MR (*left panel*), and those with MR (*right panel*) before and after surgery.

in patients with MR may account for the differences in regression of hypertrophy between these two groups of patients. Afterload was reduced in patients with AR following surgery but may be increased in patients with MR due to removal of the low impedance outflow through the regurgitant mitral valve.

These differences in left ventricular work induced by regurgitation at the mitral and aortic valves are consistent with earlier animal studies by Braunwald and colleagues. They showed in acute canine preparations that AR was associated with a marked increase in integrated left ventricular tension as left ventricular volume and filling pressure increased while, with the induction of MR, left ventricular volume and filling pressure increased in a similar manner but integrated left ventricular tension did not change. In fact, in comparison with controls, left ventricular pressure and tension decreased during the later portion of systole in the MR experimental preparation. Since left ventricular hypertrophy is, at least in part, related to left ventricular wall tension, greater degrees of hypertrophy would be expected in patients with AR as compared to those with MR and more regression expected following valve replacement in patients with aortic valve disease.

There are few angiographic studies which have evaluated patients with quantitative techniques before and following surgery for MR. Hildner and associates[1] made a nonquantitative estimation of left ventricular contractility before and after valve surgery. Of six patients with MR, one showed no change and five were judged to have decreased contractility postoperatively. Vokonas and colleagues[11] studied two patients with MR who had low preoperative EF. Both patients had decreased EF following surgery. Bolen and Alderman reported three patients with MR with EF less than 40 per cent before surgery. Each of these patients had a poor outcome, with two dying in the perioperative period and one dying nine months following surgery of heart failure.

Developments in echocardiographic techniques have made possible frequent serial observation of left ventricular chamber dimensions and wall thickness in patients before and after surgery. Although there are inherent problems in determining left ventricular volume and mass from single probe studies, utilizing the patient as his own control and evaluating changes in these measurements over time yields useful information not available previously.

A study utilizing echocardiographic techniques for estimating ventricular volumes and wall thickness has recently been reported by Schuler and colleagues. They compared these measurements before and one week, four months, and 12 months after surgery in 14 patients with mitral regurgitation and in 17 patients with aortic regurgitation. The patients with mitral regurgitation had a reduction in ejection fraction from 64 ± 3% preoperatively to 58 ± 2% in the late follow up period, while those with aortic regurgitation had a modest increase in ejection fraction. They

concluded that restoration in left ventricular function was greater following aortic valve replacement than mitral valve replacement for primary regurgitant lesions of equal severity Pritchard and co-workers have also evaluated left ventricular performance before and one week after aortic and mitral valve replacement with echocardiographic techniques. They concluded that left ventricular performance does not change initially after valve replacement for aortic valve disease and MS, but LV performance decreases significantly after surgery for MR.

In summary the surgical treatment of MS and MS-MR has little effect on left ventricular performance Surgery for MR results in only a small decrease in stroke work and resulted in no regression in left ventricular hypertrophy as observed over a relatively short follow up period. The increase in afterload which may result from mitral valve surgery is probably causally related to the reduction in left ventricular pump function observed in some MR patients following surgery

Surgery for MR cannot be expected to improve left ventricular performance and should, therefore, be applied with caution in patients with significantly reduced left ventricular pump function as judged by a low preoperative EF

Summary

Nineteen patients with mitral valve disease were studied before and a mean 11 months ± 9 months following valve replacement or reconstruction, which resulted in good postoperative valve function Biplane left ventricular angiography and pressures were utilized to determine end-diastolic volume/M (EDV) end-systolic volume/M. (ESV) ejection fraction (EF) left ventricular mass/M (LVM) and stroke work/M (SW)

There were 19 patients—six with mitral stenosis (MS) six with mitral stenosis and regurgitation (MS + MR) and seven with mitral regurgitation (MR) Those with MS and MS + MR preoperatively had no significant change in left ventricular end-diastolic pressure (LVEDP) EDV ESV LVM, or EF following surgery Patients with MR had a significant reduction in LVEDP EDV SV and SW More importantly the EF fell in four of these seven patients and LVM did not decrease following surgery It is concluded that surgical treatment for MS and MS + MR had little effect on left ventricular performance Following surgical treatment for MR, reduction in EDV is not associated with reduction in LVM, and frequently left ventricular performance deteriorates as judged by the EF

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Clinical and hemodynamic results after combined aortic and mitral valve replacement with the Lillehei Kaster pivoting disc valve

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Since its introduction in 1969 the Lillehei Kaster pivoting disc prosthesis has been implanted into 40,000 patients with valvular heart disease. Isolated replacements in the aortic or mitral position were the most common procedures. The clinical and hemodynamic results have been evaluated from this clinic, and more recently in early as well as late postoperative studies from other centers,[1-4] and showed good to excellent hemodynamic performance in the mitral and aortic position. A higher than ideal gradient, however was noted in those adult patients in whom the smallest sizes were utilized (No. 14 and No 16) for aortic valve replacement, while there were no significant differences in diastolic gradients or flow between the various sizes of *prosthesis adopted for use in the mitral position*

Thus, while the results of replacement of a single valve with this type of prosthesis are well known, very little data about the valve used in combined aortic and mitral valve replacement have yet been available. We report here the early and late clinical and hemodynamic results obtained in a study of a total of 23 unselected patients after double valve replacements.

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Material and methods

Between November 1973, and September 19 6, a total of 23 unselected patients underwent combined mitral and aortic valve replacement with the Lillehei-Kaster prosthesis (Department of Cardio-Thoracic Surgery Rikshospitalet). Four patients had undergone previous mitral valve surgery (commissurotomy), while aortic valve surgery had not been performed before in any of the patients. There were 15 women and eight men. The age of the patients ranged from 41 *to 72 years (mean, 55.3 years)*

All patients had preoperatively significant symptoms due to valvular heart disease. Physical findings indicated mitral and aortic valvular disease in each patient. Nineteen patients (83 per *cent) belonged to New York Heart Association* Class III to IV and four were in Case II. All patients had moderate to severe cardiomegaly with heart volume ranging from 500 to 1,010 ml. per square meter of body surface area, with a mean of 735 per square meter of body surface area. Fourteen patients (16 per cent) were in atrial fibrillation.

Each individual had a cardiac catheterization preoperatively and the interval between the study and surgery was from 1 to 24 months (mean, 8.3 months). The main preoperative hemodynamic findings were mean right atrial pressure of 3.6 (0 to 7) mm. Hg, mean pulmonary artery mean pressure of 29 1 (16 to 60) mm. Hg, and mean left atrial pressure (pulmonary wedge pressure) of 18.6 (9 to 34) mm. Hg. The mitral lesion varied from pure stenosis to pure insufficiency and included mixed pathology in several.

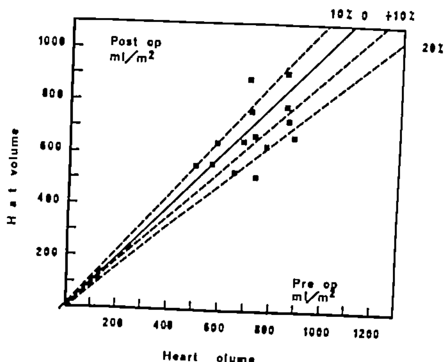


Fig. 1 Heart volume in upright position before nd after combined aortic and mitral valv replacement

Table I Prosthesis sizes and number implanted

Prosthesis size (I.D mm)	Orifice area (cm)	Numbe	
		Mitral	Aorti
14	1 49	0	1
16	2 01	0	11
18	2 54	0	9
20	3 14	0	2
22	3 80	11	0
25-28	4 91	12	0
Total		23	23

Ten patients had primarily aortic stenosis, all others had aortic insufficiency The cardiac output (Fick s method) was reduced in all but three patients with a mean value of 4 16 (1.9 to 6.4) L./minute The left ventricular early and end-diastolic pressure (LVEDP) usually varied within normal limits. The hemodynamic studies were carried out in the supine position All pressures were referred to the fourth intercostal space in the anterior axillary line

At the restudies, retrograde catheterization to the root of the aorta was performed while left ventricular catheterization was done transseptally in combination with complete right heart catheterization, using a modified Ross needle and Kifa F8 end hole radiopaque catheter By the aid of fluoroscopy in multiple projection the cath could be passed through the largest opening of mitral valvular prosthesis into the left ventr In patients with sinus rhythm, the height of LVEDP was identical with the level of the waves recorded in the left atrium Cinerecordi 35 mm 50 frames/sec. and in two cases 100 X 1 mm. cut film 6 films/sec. were obtained in prop projections, studying the movement and fun tioning of the valve prosthetics both with an without contrast medium injections (Isopaq Coronar) It was possible to profile the valve rin and the disc in the aortic position, while this wa difficult in some cases with the prosthesis in the mitral position Here however a projectio perpendicular to the plane through the base of the prosthesis could be obtained.

In the aortic position the maximum openi angle of the disc could be measured and the presence of paravalvular leakage or regurgitatio could be assessed as well.

The peak gradient across the aortic valve wa taken as the difference between peak systolic pressure in the left ventricle and aorta, whil mean systolic pressure difference was obtained by planimetry on the simultaneous recordings of central aortic and left ventricular pressure The hydraulic valve area of the aortic prosthesis wa calculated by the formula of Gorlin and Gorlin

The diastolic gradient across the mitral valve was determined by integration of the left ventricular diastolic pressure and superimposed left atrial pulse.

Operative procedure. A Rygg Kyvsgaard bubble oxygenator was used for extracorporeal circulation. Non hemic priming with moderate hemodilution (hematocrit 25 to 30 per cent) and profound local cooling with Ringer-acetat (0 to 4 C) were used. *Anoxic cardiac arrest was achieved* by aortic cross-clamping. The mitral valve was replaced first, thereafter the aortic valve without release of the aortic clamp. The largest possible prostheses were inserted. A supra annular position of the mitral prosthesis was preferred in the *majority of cases. In all cases the largest opening* of the disc valve was orientated posteriorly. The aortic valve prosthesis was placed with the largest opening pointing anteriorly and to the right or towards the commissure between the non-coronary *and the right coronary cusp. The mean aortic cross-clamping time was 75 minutes.*

Valve sizes. The basic design of mitral and aortic Lillehei Kaster prosthesis is the same. The valve sizes used are presented in Table I.

Statistics. The results are expressed as mean ± standard error of the mean (S.E.). *Student's t test for paired data* was used when comparing results from the same individual. Otherwise t test for unpaired data was used. P values higher than 0.05 were not considered significant.

Results

Hospital mortality and complications. Two patients died in the operating room. The cause of death was in both cases "left ventricular pump failure," which was resistant to all therapy including intra aortic balloon counterpulsation. There were no other deaths during the first 30 days following surgery, resulting in a hospital mortality rate of 8.7 per cent. Two patients developed left ventricular pump failure during the early postoperative course, but they were

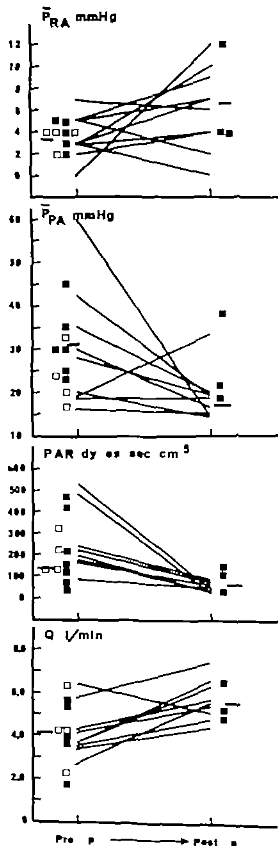


Fig. 2.

Fig. 2. Right atrial mean pressure ($\bar{P}_{RA}$), pulmonary artery mean pressure ($\bar{P}_{PA}$), pulmonary vascular resistance (*PVR*), and cardiac output (*Q*) before and after combined aortic and mitral valve replacement. *Solid line* is drawn between values in patients in whom pre- and postoperative values are available. *Horizontal lines* mark mean values. *Squares* mark values from patients who lacked either pre- or postoperative data. *Open symbols* mark patients who died.

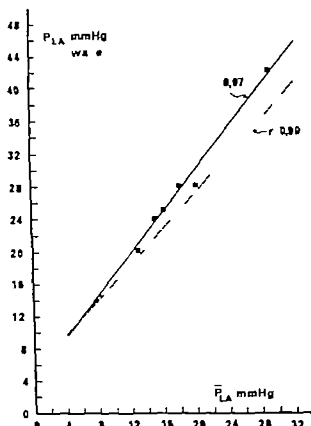


Fig. 3. Amplitude of the v-wave in left atrial pressure, P_{LA}, related to the mean left trial pressure, $\bar{P}_{LA}$, in 12 patients after combined aortic and mitral valve replacement——, regression line P —— = 1.34 $\bar{P}_{LA}$ + 4.10. —— regression line for patients after mitral valv replacement with the Björk Shiley tilting disc valve.

ccessfully treated with intra aortic balloon umping. Two patients developed severe jaun dice Otherwise there were no serious postopera tive complications. Anticoagulant therapy with warfarin was given routinely postoperatively and was continued after discharge from hospital.

Follow-up Of a total of 21 patients discharged from the hospital, three died 6 weeks, 2 months, and 33 months, respectively after the operation. The reason for death was in one case ventricular arrhythmias, in one case acute myocardial infarc tion, while one patient succumbed to heart fail ure. In these patients clinical examination had revealed no symptoms of prosthesis dysfunction. Permission to perform a postmortem examination was obtained in two patients, and showed normally functioning prostheses. A total of 18 patients were alive at the time of restud The follow-up period was from 13 to 40 month an 24.4 months)

Clinical findings. None of the pa ie d mon strated signs or symptoms of congestive hear failure. Changes in functional capacity demonstrated an improvement of one class or more (N.Y.H.A. Classification) in 12 patients (67%), while the others were unchanged with the exception of one patient whose condition had worsened. Atrial fibrillation was persistent in eight patients, and had reverted to sinus rhythm in two. The opening and closing sounds of the disc were heard in all patients, and in most of them a low grade systolic ejection murmur was characteristic, and was best heard along the left sternal border. In one patient a faint diastolic murmur was heard in the same area.

Late arterial thromboembolic complications. There had been three cases of cerebral embolism, leaving only minor neurological complications. Thus 17 per cent of the patients had had episodes of systemic embolism during the follow-up. The total follow-up period was 439 months. Hence the incidence of late arterial thromboembolic complications was 3 × 1200/439 = 8.2 incidences per 100 patient years. None of the patients had suffered from thrombotic valve malfunction.

Radiological heart volume (Fig 1) Radiological heart volume before operation and at the restudy was available in all 21 patients. The mean heart volume was significantly reduced from 721 ± 26.9 to 624 ± 37.9 ml. per square meter body surface area (t = 2.43, $0.05 > p > 0.01$). Eight patients had no change in the size of the heart (±10 per cent) and one patient had a larger heart at the restudy. Decreases of more than 20 per cent of the preoperative value were observed in 6 out of 18 patients (33 per cent).

Central hemodynamics. The postoperative hemodynamic studies included combined left and right-sided heart catheterization. Four patients were unwilling to be recatheterized. In 1[illegible] patients, a transseptal catheterization of the left atrium for pressure recordings was possible. The transseptal approach of the left heart failed for technical reasons in two patients, and pulmonary wedge pressure was taken as representative of the left atrial pressure.

Comparison between the hemodynamic data pre- and at the postoperative control, all obtained in a resting basal state, is presented in Fig. 2. The *mean right atrial pressure* was normal or slightly elevated before surgery and tended to be slightly higher at the restudy increasing from 3.5 ± 0. [illegible] to 6.1 ± 1.2 mm. Hg (t = 1.79, $p > 0.05$), in th

Table II Postoperative measurements of prosthesis gradients

Position	Prosthesis size (I.D. mm.)	Number of patients	Prosthesis gradient (mm. Hg) Peak	Mean
Aortic	16	6	11	21
	18	5	12	16
	20	1	6	4
Mitral	22	4		5
	25	7		5
	27	1		13

patients in whom comparable data were available. *The pulmonary artery mean pressure* which was elevated in approximately one-half of all patients examined before operation, fell from an average of 30.1 ± 4.5 to 18.8 ± 1.9 mm. Hg ($t = 2.02$, $p > 0.05$) and was within the normal range in all but two patients. The preoperative *pulmonary vascular resistance* was significantly reduced from a mean value of 258 ± 57.2 to 45 ± 10.0 dynes sec. cm. ($t = 3.58$, $0.05 > p > 0.01$) *Cardiac output was* greater than preoperatively in all patients with one exception, and increased significantly from a mean value of 4.19 ± 0.40 to 5.62 ± 0.32 ($t = 3.33$, $0.05 > p > 0.01$) Normal values for cardiac output (> 5.0 L./minute) were found in nine of 12 patients. *The arteriovenous oxygen difference* which was elevated in most patients before surgery indicating a hypokinetic circulation, was reduced from a preoperative mean value of 53.0 ± 2.8 ml./L. to 39.0 ± 3.0 ml./L. ($t = 3.65$, $0.05 > p > 0.01$)

An elevated *left atrial pressure* was seen in several patients before operation, depending on the degree of mitral stenosis and left ventricular failure. After operation, left atrial pressures were elevated (> 12 mm. Hg) in all patients with an average of 19.2 ± 5.4 mm. Hg) The elevated left atrial pressure was accompanied by a marked increase in left atrial a wave. The relationship between the amplitude of the left atrial v wave and the mean left atrial pressure is shown in Fig. 3, where a close correlation is observed.

Regarding left ventricular *early diastolic* and *end-diastolic pressure* (LVEDP) there were considerable individual variations when comparing pre- and postoperative findings (Fig. 4) Both

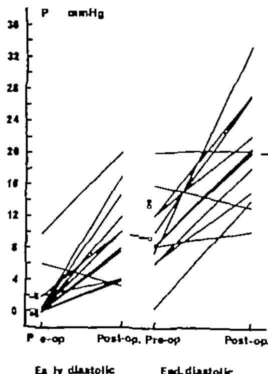


Fig. 4. Left ventricular early and end-diastolic pressure (LVEDP) before and after combined aortic and mitral valve replacement. Symbols as in Fig. 2.

parameters, however tended to be higher after surgery than before. Early diastolic pressure increased significantly from 1.7 ± 0.9 to 9.6 ± 1.6 mm. Hg ($t = 4.91$, $p < 0.01$) and LVEDP increased significantly from 9.3 ± 1.5 to 19.4 ± 1.9 mm. Hg ($t = 4.68$, $p < 0.01$)

Valve gradients. Simultaneously pressure recordings from the left ventricle and the aorta disclosed no peak systolic pressure gradient across the aortic prosthesis in three patients, while nine patients had a gradient varying between 2 and 33 mm. Hg. The mean peak gradient was 11.1 mm. Hg. The systolic mean gradient across the aortic valve varied between 8 and 30 mm. Hg, with a mean value of 17.2 mm. Hg. Two patients had no diastolic gradient across the mitral prosthesis, while the remaining 10 patients had an early diastolic gradient varying between 3 and 13 mm. Hg. The mean diastolic pressure gradient was 6.0 mm. Hg. There was no definite relationship between gradient and mitral valve prosthesis sizes, while the smallest prostheses (No. 16) in the aortic area tended to have higher gradients than the larger sizes (Table II)

The effective aortic valve orifice area calcu



Fig 5 A and B. Angiographic study with aortic root injection. A Systole. The disc opening posteriorly Flow through large opening only Maximum opening 60 degrees. B Diast le. Very small regurgitation through the aortic valve prosthesis—almost invisible. Not the angle between the disc plane and the valvular ring plane in the closed position (about 18 degrees). No paravalvular leakage.

lated according to the Gorlin formula varied between 1.60 and 4.04 cm. with a mean of 2.19 cm. As it was impossible to obtain simultaneous pressure recordings from the left ventricle and left atrium, the effective mitral orifice area could not be calculated.

Angiographic studies In all cases a small mitral regurgitation was observed at aortic root injection of the contrast medium No case of paravalvular leakage or thrombus formation on the valve prosthesis was seen Maximum opening angle of the disc was measured to slightly more than 60 degrees in all cases when measuring the net opening angle between the closed position and fully open position (Fig. 5A). During diastole, very small and almost invisible regurgitation was seen through the aortic prosthesis (Fig. 5B) Note the angle between the disc plane and the valvular ring plane in the closed position (about 18 degrees)—no paravalvular leakage. A transseptally introduced catheter passed through the larger opening of the mitral prosthesis into the left ventricle is shown in Fig 6.

Discussion

The results of the present study show that combined aortic and mitral valve replacements with the Lillehei Kaster disc valve prosthesis can be performed with a relatively low mortality rate. Hospital mortality rate (8.7 per cent) was comparable with that recently reported in studies after double valve replacement with the Bjork-Shiley disc valve prosthesis.[8-10] Terzaki and co-workers, using a caged ball valve, noted a higher surgical risk after double valve replacement, in particular in patients with bivalvular stenosis. It is possible that the increased mortality rate reported with the caged-ball valve was attributed in part to dysfunction of the mitral prosthesis related to a hypertrophied left ventricle with a small chamber[12] and that the disc valve with its low profile in this connection represents an improvement in valve design. In our study no single preoperative hemodynamic measurement could be used to predict the importance of deranged ventricular function on the outlook for the patient, and it has rarely been found by others. The two-year survival rate of 78 per cent compares well with results previously referred in series of patients after double valve replacement with other types of prostheses.[8, 14]

The findings in the follow-up study demonstrate that replacement of both the mitral and aortic valves is an effective mean for reducing

cardiac disability in patients with severe malfunctions of these valves. In each patient studies carried out postoperatively indicated marked improvement in the hemodynamic abnormalities present before surgical treatment. At rest the pulmonary artery pressure, pulmonary vascular resistance, and cardiac output were normal or near normal in most instances. Diastolic pressure gradients across the prosthetic mitral valve were present, but of the same magnitude as previously found with the Lillehei-Kaster prosthesis in the single mitral position.[4, 14] A systolic pressure difference between the left ventricle and the aorta was found in the majority of patients. The systolic pressure gradients were in general smaller and the calculated functional valve area in general larger than previously reported after single valve replacement with the Lillehei-Kaster prosthesis.[1, 4, 14, 17] Nonetheless, higher than ideal gradients (up to 33 mm. Hg) were noted in patients in whom the smaller sizes for aortic valve replacements had been used.

The increase in the early diastolic and end diastolic left ventricular pressures is at variance with observations made after single aortic valve replacement.[17] Mason and associates found that after combined aortic and mitral valve replacement with the caged-ball valve, LVEDP declined to normal levels in patients in whom it was abnormally elevated before operation. A rise in LVEDP similar to that in the present study was, however reported by us in patients with double Björk-Shiley disc valve prosthesis.[19] The high filling pressure in the left ventricle most probably reflects persistent changes in the elastic properties of the myocardium secondary to longstanding and irreversible myocardial disease. Under such conditions, a rise in cardiac output obtained after replacement of the diseased valves will be associated with a rise in left ventricular filling pressure due to reduced compliance. The possibility of additional cardiac damage during cardiopulmonary bypass and open heart surgery with a relatively long cross-clamp time plus cardiac arrest must also be mentioned in this connection.

One of the design goals in the development of the Lillehei-Kaster prosthesis was to improve the lateral flow valves (ball, conventional disc) by an approach to central flow with the disc opening angle of 80 degrees.[19] Our study shows that the maximum opening angle was smaller and was measured to only slightly more than 60 degrees in



Fig. 6. Right anterior oblique projection. Transseptally introduced catheter through larger opening of the mitral valve prosthesis into the left ventricle.

all cases. The motion analyses of the disc by high-speed cine filming carried out by Sigwart and co-workers[9] in their patients with aortic or mitral prosthesis also indicate that the opening angle of the disc varies between 56 degrees and 77 degrees and does not reach the maximum of 80 degrees. Less than total opening of the disc in the absence of any dysfunction was also apparently noted by Haerten and co-workers.[20] This phenomenon was not previously noted in any of the in vitro pulse duplicator studies. Explanations for the discs not reaching their optimal opening angle in vivo are speculative at this time. The findings, however are of distinct interest to the hemodynamic performance, since the large opening angle of the disc was meant to compensate for a relatively thick sewing ring.

Pressure recordings from the left atrium showed in general an elevated mean left atrial pressure with high v wave. There was a strong relationship between the amplitude of the v waves and mean left atrial pressure. The high v waves observed in the left atrial curve do not necessarily indicate regurgitation of blood from the left ventricle to the left atrium. An almost identical relationship between amplitude of the

v wave and mean left atrial pressure was also found after isolated mitral valve replacement with the Bjork-Shiley prosthesis in the absence of clinical or angiographic signs of mitral regurgitation. Reflux from the ventricle to the atrium is the only one of several factors contributing to the generation of v wave in the left atrium. The inflow of blood into the left atrium, propagation of the pulmonary arterial pulse wave, and different actions of the mitral valve are also probable factors contributing to the generation of a v wave after mitral valve replacement.

Early postoperative arterial thromboembolic complications which may occur relatively frequently after aortic valve implantation[11-14] were not seen in the patients studied by us. This cannot however be used as an indication of the thrombogenic nature of the valve itself since the early formation of arterial thrombi is also influenced by the surgical procedure, extracorporeal circulation, and by the postoperative treatment. In the present study 8.3 late arterial thromboembolic complications occurred per 100 patients per year. All of them were cerebral, which may reflect the real distribution. The late incidence of arterial thromboembolic complications after combined aortic and mitral valve replacement with the Lillehei Kaster prosthesis has not been evaluated by others, but our figures do not differ significantly from the incidence of 6.1 per 100 patients per year after isolated aortic valve replacements with the same prosthesis. In four other studies of patients with combined aortic and mitral valve replacements with other types of prosthesis, the annual rates of thromboembolic complications have varied between 0 and 4.0 per 100 patients per year.

Summary

Combined mitral and aortic valve replacement with the Lillehei Kaster pivoting disc valve prosthesis was performed in 23 patients. Hospital mortality rate was 8.3 per cent. Detailed postoperative clinical and hemodynamic studies were performed after a mean follow up period of 24.4 months. Replacement of both valves had resulted in a marked symptomatic and hemodynamic improvement with a normal or nearly normal resting value of cardiac output, pulmonary arterial pressure, and pulmonary vascular resistance, while left ventricular end-diastolic pressure (LVEDP) had increased significantly. The rise in left ventricular end-diastolic pressure most probably might be related to the simultaneous rise in cardiac output (Starling mechanism), reflecting the severity and irreversibility of the underlying myocardial disease. Most patients also had systolic gradient across the aortic prosthesis, as well as diastolic gradient across the mitral prosthesis. The gradients across the mitral prosthesis were approximately the same as seen after single valve replacement, while the pressure gradients across the aortic prosthesis were somewhat smaller than previously reported. Angiographic studies of the aortic valve movement indicated that the opening angle of the disc was approximately 60 degrees and thus less than according to the valve specifications.

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Unidirectional complete heart block

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Apart from being an electrophysiological fantasy intact ventriculoatrial (VA) conduction in the presence of antegrade complete heart block (CHB) may indicate absence of a "fixed discrete constant" lesion, a logic to which credence is lent by intermittent conversion of rhythm to normal sinus. His bundle electrocardiography by virtue of its ability to pick those with concealed retrograde conduction, has proved true the prophecy of Scherf and Cohen, who while reporting 81 cases of such a phenomenon felt that its incidence was higher than the world literature suggested. Such patients were frequently missed on scalar electrocardiography

Retrograde conduction may either be in the fully manifest form with changed P" wave configuration and vector discernible on surface ECG or in the concealed form unmasked by HBE when an AH interval following a ventricular beat shows prolongation usually in inverse proportion to the coupling interval between the QRS and P" wave. Retrograde conduction can also be deduced if an H spike in the HBE is inscribed prior to atrial potentials of high atrial leads.

This paper presents the observations in 42 patients with CHB, with 22 cases showing evidence of retrograde conduction proved by HBE. Existing literature on the subject is reviewed and various theories to explain the phenomenon are discussed

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Material and methods

The first consecutive 42 patients suffering [...] CHB who were subjected to electrophysiolo[...] studies between March, 1975 and June, 1977 [...] presented. There were nine females and the [...] of the patients ranged from 32 to 85 years ([...] 55.8 years) All patients were symptomatic [...] none was found to have an organic heart [...] At no time did the ECG of any patient show [...] conducted beats.

HBE was performed by the method essenti[...] similar to that described by Scherlag [...] colleagues. Following right antecubital ven[...] tion, two bipolar electrode catheters were in[...] duced under fluoroscopic vision. The tip of [...] was placed in the high right atrium (HRA) [...] recording an intra-atrial electrogram (IAE), [...] the tip of the second catheter was advanced [...] the right ventricular apex for pacing purpo[...] HBE was recorded by a bipolar catheter pl[...] across the tricuspid valve after its introduction [...] percutaneous puncture of the femoral vein [...] patients, and via right the antecubital vein in [...] patients. In two other subjects, HBE record[...] were made by placing the catheter near the a[...] valve after its insertion percutaneously from [...] femoral artery HBE was recorded using stand[...] frequency filters of 40 to 500 Hz on an Electro[...] for Medicine multichannel photorecording [...] tem or on a Sanborn direct writer at a paper sp[...] of 100 mm./second. In the event of VA cond[...] tion, a 12 lead scalar ECG was also recorded [...] study the P wave polarity

After recording basal HBE, ventricular pac[...] was done using a KM cardiac pacemaker at tw[...] diastolic threshold current output. In [...]

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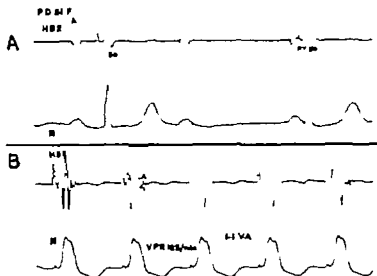


Fig. 1 A and B. *A*, Simultaneous tracings of His bundle electrogram *(HBE)* with ECG Lead II showing complete heart block (CHB). HBE shows fixed HV interval of 60 msec. with AH dissociation suggesting block at the level of the AV node. *B*, *HBE and ECG Lead II during ventricular pacing at the rate of 125/min. showing 1:1 VA* conduction. (Paper speed 100 mm./sec.)

presence of VA conduction, incremental ventricular pacing was done until VA Wenckebach block developed. The records were also analyzed for evidence of concealed ventriculo-nodal conduction.

Results

In our series of 42 patients, evidence of retrograde conduction was present in 22 patients (52.4 per cent). It was manifest as VA conduction in 15 (35.7 per cent) and as concealed ventriculo-nodal (VN) conduction in seven (16.6 per cent) (Table I).

Supra-Hisian block. Three of nine patients with complete atrioventricular (A V) nodal block revealed evidence of 1:1 VA conduction (Fig. 1). Incremental ventricular pacing resulted in the development of VA Wenckebach periods at ventricular pacing rates (VPR) of 110 and 122 per minute, and in the third case 1:1 VA conduction was recorded at VPR up to 133 per minute. Attempts on higher pacing rates were given up as the patient developed angina. VA conduction time ranged from 110 to 130 msec., with a mean of 120 msec. in this group.

Intra-Hisian block. This group consisted of 11 patients, of which six (54.5 per cent) showed evidence of retrograde conduction. Four of these had manifest VA conduction (Fig. 2) and in two

Table I

Type of CHB	*No. of cases*	*Manifest VA*	*Concealed VA*	*Total VA*
Supra-His	9	3	—	3 (33.3%)
Intra-His	11	4	2	6 (54.5%)
Infra-His	22	8	5	13 (58.7%)

more there was evidence of concealed VN conduction. In one patient with VA conduction with intra-Hisian CHB retrograde split H potentials were interspersed between QRS and retrograde P" wave during ventricular pacing. VA conduction in this group varied between 110 to 140 msec. with an average of 122 msec. One patient in this group who had prolonged AH of 140 msec. during basal HBE had a VA conduction time of 120 msec., the same as other patients with normal AH. This patient developed Wenckebach VA block at VPR of 130 per minute.

Infra-Hisian block. This is the largest group comprising 52 per cent of all cases of CHB. Ventricular pacing revealed 1:1 VA (Fig. 3) in eight patients (36 per cent), and in an additional five patients (22.7 per cent), there was evidence of concealed VN conduction (Fig. 4), with the overall incidence of 58.7 per cent retrograde conduction in infra-His CHB.

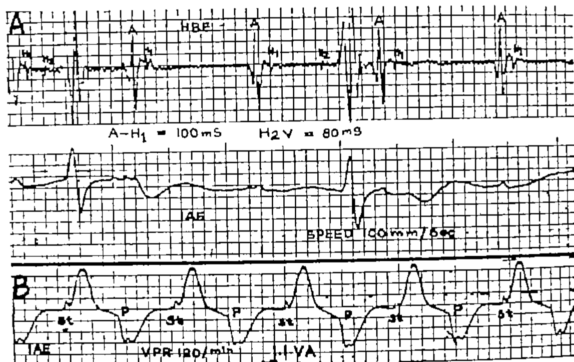


Fig. 2. A and B. *A*, HBE and low right trial electrogram in patient with CHB and narrow QRS. (Atrial rate 110/min. and ventricular rat 60/mm.) Each A potential is followed by H deflection with an AH, interval of 100 msec. and each "V" potential is preceded by H_2 deflection with an H_2V interval of 80 msec. This suggests that in addition to intra-His CHB there is conduction delay in the distal His-Purkinje system. *B* High right atrial electrogram of the same patient during ventricular pacing at the rate of 120/min. with 1:1 VA conduction. (Paper speed 100 mm./sec.)

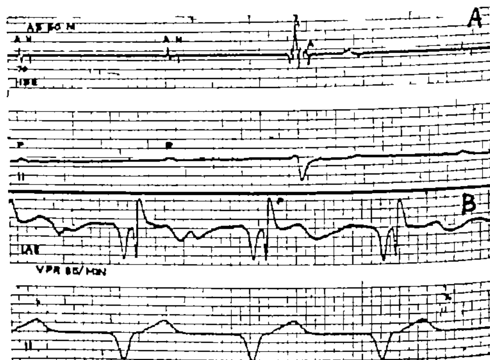


Fig. 3 A and B. *A* HBE and ECG Lead II showing CHB with fixed AH interval of 50 msec. with HV dissociation diagnostic of infra-His CHB After tw consecutiv AH deflections, the third A deflection following ventricular depolarization is not follo ed by H poten al because of concealed entriculonodal conduction. *B*, IAE and ECG Lead II during ventricular pacing t the of 8 /min showing 1 1 VA conduction. This represents unidirectional infra-His CHB. (Paper speed 100 mm ~)

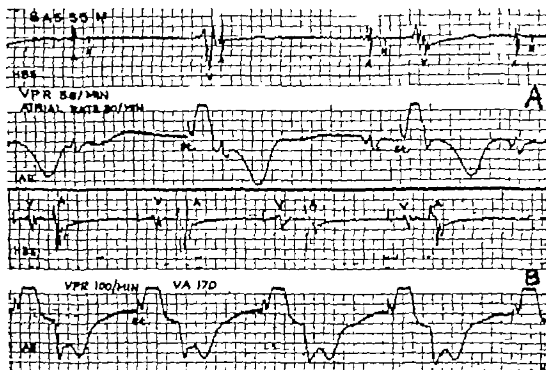


Fig. 4. A and B. A, HBE and IAE in patient with infra-His CHB with no idioventricular escape rhythm and on ventricular pacing at the rate of 56/min. The second A deflection following V potential is not accompanied with H deflection due to concealed ventriculonodal conduction. B, HBE and IAE during ventricular pacing at the rate of 100/min. with 1:1 VA conduction. (Paper speed 100 mm./sec.)

Concealed conduction. Concealed retrograde VN conduction as reflected by prolongation of A H interval following ventricular excitation was present in seven patients with intra- and infra His CHB. Several such sequences were analyzed and it was observed that with a decreasing R P interval (the interval between the QRS and the following sinus P wave) there was a progressive increase in the A H/A H (proximal) interval until at a critical R P interval the H deflection dropped off. In a few of these patients, a retrograde H deflection could also be seen, suggesting that the retrograde conduction may also be through the HB and not through any bypass pathway. (This phenomenon was also studied in a normal subject where ventricular pacing at a rate faster than the sinus rate induced obligatory A V dissociation.)

Discussion

Retrograde conduction in the presence of complete AV block may follow ventricular automatic beats, ventricular extrasystole, or ventricular pacing and may be either manifest or concealed. In the fully manifest form, an aberrant P'' wave configuration and vector may appear on the surface ECG. In 1964 Scherf and Cohen reported 81 cases of unidirectional CHB from the world literature. But now with the help of HBE, more and more patients have been found to have VA conduction in the presence of complete antegrade heart block. Concealed retrograde conduction can be more successfully reflected in the HBE when it causes prolongation of AH interval of the next sinus beat.

Since our series was small, the incidence of unidirectional CHB is probably higher than reported elsewhere. Puech gave its incidence as 16.7 per cent from a series of 185 cases. Factors which might give a higher index of suspicion of unidirectional CHB and which might reveal a VA conduction responsible for this higher incidence are the elicitation of the phenomenon after right ventricular apical pacing at various rates and at a higher mean age in our group of patients.

VA conduction was most frequently encountered in patients with CHB due to infra His lesions. Puech[1] also made similar observations and described it in 43.2 per cent of all patients with infra His CHB.

Retrograde His bundle deflection cannot be

made out early in every case and is usually obscured within the V complex. It need not imply that VA conduction is occurring through the bypass pathway the presence of which is refuted by the phenomenon of concealed retrograde conduction and the development of Wenckebach periods in VA conduction during incremental ventricular pacing. Therefore, HBE has not proved as fruitful as anticipated in the study of VA conduction.

The ultimate difficulty arises in explaining the phenomenon of unidirectional CHB Various mechanisms hypothesized are "increased irritability of the atrium causing it to contract due to mechanical stretch induced by ventricular systole" the presence of abnormal centers in the lower atrial region getting triggered by ventricular contraction others feel it is due to the influence of the geometrical structure of the lesion in relation to the propagation of the impulse the electrotonic propagation of the impulse from one part to the other of a highly localized lesion, and the presence of dual AV nodal pathways within the His bundle and AV node.

Summary

Forty two patients with complete heart block were subjected to electrophysiological studies wherein apart from localization of the site of the conduction defect, ventricular pacing was done to assess ventriculo-atrial (VA) conduction and concealed ventriculo-nodal (VN) conduction. There was evidence of retrograde conduction in the presence of orthograde CHB in 22 patients (52.4 per cent) Fifteen patients (35 7 per cent) had VA conduction and seven (16.6 per cent) had concealed VN conduction. In patients with supra Hisian CHB three of the nine patients had VA conduction while of the 11 patients with intra Hisian CHB six had retrograde conduction (four with VA and two with concealed VN conduction) In the infra Hisian CHB group of the 22 patients, eight had VA conduction and five had concealed conduction.

Incremental ventricular pacing induced VA Wenckebach periods at VPR from 110 to 133/minute with a VA interval of 110 to 130 msec In view of the induction of Wenckebach VA the recording of retrograde H potentials cases, and relatively long VA conduction is surmised that retrograde conduction presence of orthograde CHB takes place the AV conduction system.

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Postpartum cardiac failure—heart failure due to volume overload?

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The development of heart failure without any obvious cause after a pregnancy in a previously healthy woman is now a well recognized although rare event, and it is generally accepted that there is a specific heart disease of the puerperium.[1-3] In Zaria, this condition accounts for almost 10 per cent of female admissions in our hospital at certain times of the year and although like others we have called this peripartum cardiac failure (PPCF) nearly all our patients develop symptoms postpartum.[4-6] The clinical picture differs from the typical cases previously described[1-3] because edema (including facial) is gross, treatment is rapidly effective in nearly all patients, and there are very few relapses. The purpose of the present study was to try to assess myocardial function in these patients to determine if there was severe heart muscle failure or not.

Patients and methods

Patients. Forty three patients who presented to the hospital with the typical features of PPCF within 6 months of delivery were studied. All patients had carried out the usual Hausa tradition of taking food rich in added salt and lying on heated beds during the postpartum period for at least 40 days. Patients with severe anemia (PCV < 25 per cent) organic valvular heart disease, long-standing cardiomegaly toxemia, chronic renal disease, or fever were excluded. On admission all patients were examined and weighed. A chest radiograph and electrocardiogram were done and the PCV was checked. The clinical features of the patients are shown in Table I. All patients were treated with diuretics and digoxin. Twenty-seven patients were restudied during the convalescent period (mean interval of 15 days

Table I Clinical data on admission (43 patients)

Age: Mean 24 years (range 15 to 38 years)
Number of previous pregnancies: mean 3; 6 primigravida
History of previous postpartum swelling: 1 patient
Time from delivery to presentation: mean 2.26 ± 1.3 months
Symptoms and signs:
Shortness of breath and edema: all patients
Jugular venous pressure: raised in all patients (mean 9 ± 2.4 cm.)
Heart rate: 116 ± 15 beats per min.
Blood pressure: systolic, 129 ± 20 mm. Hg; diastolic, 98 ± 16 mm. Hg
Systolic murmur at apex: 16 patients
Gallop rhythm: 32 patients
Pleural effusion: 16 patients
Ascites: 32 patients
Investigations:
Weight: 55.5 ± 8 Kg.
PCV: 37 ± 7%
Cardiothoracic ratio: 0.62 ± 0.06
Electrocardiogram: Sinus rhythm—all patients
T wave inversion widespread: 19 patients
T wave inversion lateral chest leads: 12 patients
Others: 5 (3 bundle branch block; 2 small complexes)
Normal: 1 patient

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after admission range 5 to 51 days) Twelve normal Nigerian subjects were also studied.

Methods

Echocardiography All patients had an echocardiogram done on admission using the Electronics for Medicine V3270 ultrasonoscope (frequency 2.23 MHz, repetition frequency 1,000 sec) The output was displayed on an Electronics for Medicine multichannel stripchart recorder at a paper speed of 50 mm. sec. with a simultaneous electrocardiogram and phonocardiogram. The technique used has been described before. Measurements of the left ventricular dimension were only made on those recordings showing clear continuous echoes from the septum and posterior wall (41 patients)

Analysis of the echocardiograms. The recordings were analyzed in the usual fashion. Left ventricular volumes were estimated by the method of cubing the dimension. It was recognized that this overestimates the volume of a large cavity and that individual values are only an estimate but it is sufficiently accurate for studying groups of patients. The usual indices were used to assess left ventricular function and were given by the following formulae[11]

$$\text{fractional shortening} = \frac{EDD - ESD}{EDD}$$

mean velocity of circumferential fiber shortening

$$(\text{Mean Vcf}) = \frac{EDD - ESD}{EDD \times ET}$$

$$\text{ejection fraction} = \frac{FDV - ESV}{EDV}$$

where FDV = end-diastolic volume, ESV = end systolic volume EDD = end-diastolic dimension, ESD = end systolic dimension, and ET = ejection time derived from the externally recorded carotid pulse and the aortic valve echogram if available A diagnosis of pericardial effusion was only made if there was a clear posterior echo-free space between the left ventricular epicardium and pericardium with flattening of the normal movement of the pericardium, and disappearance of the space behind the left atrium when a scan was made from the left ventricle to the aortic root.

Systolic time intervals. These were recorded as has been previously described, at a paper speed of 100 mm./sec. The carotid pulse was recorded by a solid state externally applied transducer and left ventricular ejection time (LVET) was measured from the onset of the carotid upstroke to the dicrotic notch. The pre-ejection period (PEP) was obtained by subtraction of the LVET from the Q-S, interval. As all the intervals are affected by heart rate, they were corrected to the appropriate systolic time index using the formulae derived by Weissler and associates.

Right heart catheterization and cardiac output determinations. Ten patients had right heart catheterization. In eight patients miniature heart catheters were used and cardiac output was measured by the thermodilution technique as described by Branthwaite and Bradley A cardiac output computer was used to integrate the total area under the thermodilution curve and instantaneously calculate the cardiac output. All thermodilution curves were recorded and those with an uneven outline were discarded. Although the cardiac output computer assumes a hematocrit of 42 per cent, no correction was made for lower values because even at a hematocrit of 3[illegible] per cent the calculated error is less than 1 per cent. Pressure measurements were made through the miniature catheters connected to a pressure transducer in the normal way In two patients Swan-Ganz balloon catheters were used and in one patient a satisfactory pulmonary capillary wedge pressure was obtained. In another two patients the miniature catheters were left in situ in the pulmonary artery and repeat cardiac output measurements were made 24 hours later. As the patients were studied sitting at 45 degrees the choice of a zero reference point was difficult. The sternal angle was chosen and a +5 mm. Hg constant was added to the pressures recorded. Since the sternal angle does not have a constant relation in all positions to the mid point of the right atrium, it is probable that the pressures are underestimated.

Results

A. On admission

Clinical data (Table I). The mean systolic (129 ± 20 mm. Hg) and diastolic (93 ± mm. Hg) blood pressures were raised. The diastolic blood pressure was less than 95 mm. Hg in only 11 patients. The cardiothoracic ratio on the chest radiograph was greater than 50 per cent in all the patients. The electrocardiograms were abnormal in all but one of the patients, with the majority showing non-specific T wave changes.

Table II. Echocardiographic data on admission (Mean ± S.D.)

Index measured	Patients (n = 41-43)	Normals (n = 12)	Normal range
1. Basic			
Left ventricular end-diastolic dimension (cm.)	5.7 ± 0.6	4.8 ± 0.4	3.5-5.7
Left ventricular end-systolic dimension (cm.)	4.5 ± 0.7	3.1 ± 0.3	2.5-3.7
Left atrium (cm.)	4.3 ± 0.7	2.7 ± 0.4	1.9-4.0
Aortic root (cm.)	2.8 ± 0.3	2.8 ± 0.4	2.0-3.7
Mitral valve mean diastolic closure rate (cm. sec.)	13.5 ± 6	13 ± 5	5-20
2. LV function			
Mean Vcf (circ. sec.)	1.2 ± 0.4	1.2 ± 0.18	1.0-1.9
Ejection fraction (%)	50 ± 13	70 ± 7	50-80
Fractional shortening	0.2 ± 0.08	0.32 ± 0.04	0.24-0.4
3. Estimated volumes			
Stroke volume (ml.)	100 ± 48	68 ± 20	50-100†
Cardiac output (liters min.)	11.4 ± 4.4	4.8 ± 1.8	2.5-6.0†

Normal range from Feigenbaum.
† = Normal data from *The Heart*, ed. by J. Willis Hurst, 1974, p. 83.

Echocardiograms (Table II). The results from the 12 normal Nigerian subjects are also shown. In our studies we have found that our normal values do not differ significantly from those of Feigenbaum.

Twenty four (55 per cent) of the patients had pericardial effusion and these accounted for the very large hearts seen on the chest radiographs of some patients.

The mean left ventricular end-diastolic dimension was at the upper limit of normal. Thirteen patients had a LVEDD greater than 6 cm., but only two patients had a dimension greater than 6.5 cm. (6.8 cm. each) (Fig. 1). Except for these two patients, the left ventricles were dilated, but not grossly so as in congestive cardiomyopathy.

The left atrium was larger than normal (4 cm.) in 28 patients (Fig. 1). The mean right ventricular end-diastolic dimension was normal (1.7 ± 0.6 cm. normal range 0.8 to 2.4 cm.). However the measurement of the size of the right ventricle by echocardiography is recognized to be inaccurate.

The indices of left ventricular function showed considerable scatter (Fig. 2). The mean values for the ejection fraction and the mean Vcf were just within the normal range, Table II. Only nine patients had a mean Vcf below 0.9 circs. sec. (Fig. 2). The two patients with the lowest mean Vcf (0.51 and 0.53, respectively) approaching the range expected if there is a severe heart muscle failure, were the only two patients who did not respond quickly to treatment and who had signs of left ventricular failure when restudied. Two other patients had low mean Vcf values (0.6 each) but they appeared to respond well to hospital treatment although they did not return for repeat measurements. There was a good correlation within individuals between the ejection fraction and the mean Vcf, (r = 0.86) (Fig. 3). Fractional shortening was depressed, possibly artificially so because of the increase in cavity size.

The estimated stroke volume was greater than 50 ml. in all patients. As the heart rates were high, the estimated cardiac outputs were also high, although there was considerable scatter. The two patients who responded poorly to treatment had lower cardiac outputs (6.6 litres min. each). The three lowest estimated outputs were in three patients who had normal LVEDDs (4.0, 4.3, and 5.0 cm.).

Systolic time intervals. (Table III and Fig. 4). There was prolongation of the PEPI (156 ± 27 msec. normal range 100 to 155 msec.), and shortening of the LVETI (373 ± 22 msec., normal range 395 to 435 msec.). The mean of the ratio PEPI/LVETI, a better index of left ventricular function, was at the upper limit of normal, 0.41 ± 0.08, (normal range 0.27 to 0.41).[14] Although the ratio increases with heart failure, half the patients had normal values and the results do not suggest there is severe heart muscl failure in all the patients.

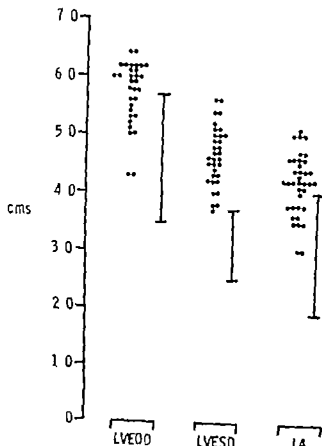


Fig 1 S (t r of nd idual alues of the basic echocar diographic mea ments LVEDD = left ventricular end diastolic dimension LVESD = left ventricular end systolic dimension LA left trial dimension *The vertical bar* represent the normal ranges

Table III Systolic time intervals on admission (mean ± S D)

Index	*Patients* (n = 43)	*Normals* (n = 12)	*Normal range*†
PEPI (msec)	156 ± 27	127 ± 20	100-165
LVETI (msec)	373 ± 22	395 ± 18	394-436
PEP/LVET	0.41 ± 0 06	0.32 ± 0.04	0 27-0.41

† = normal range from Weissler et al 1968.

Cardiac catheterization data (Table IV). All the patients had raised atrial pressures on admission. The right ventricular end-diastolic pressure was raised in all patients and all the patients had pulmonary hypertension The pulmonary artery end-diastolic pressure (an index of the left ventricular filling pressure) was also raised in all the nine patients in whom it was measured The mean cardiac output measured by the thermodilution technique for the whole group was 6.3 ± 1.5 liters min. In all patients an echocar

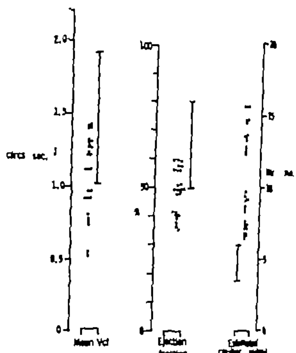


Fig. 2. Scattergram of individual values of indices of ventricular function and estimated cardiac output de from the echocardiograms. *The vertical bars represent* normal range.

diogram was done first prior to catheterization. two patients the echocardiograms were destroy due to a technical error In the remaining fo patients who also had thermodilution measure ments done the mean difference was 1.0 li min. [1] (Table V)

B Convalescent.

Clinical data. At restudy all the patients ha improved. The mean weight loss was 11.5 ± 6 kilograms ($P < 0.001$) Two patients had short ness of breath, but none had edema.

The blood pressure of these 27 patients had fallen (systolic 116 ± 15 mm. Hg. $P < 0.01$, di astolic 79 ± 15 mm. Hg. $P < 0.01$). Only three patients had a diastolic blood pressure above 95 mm Hg.

The heart rate had decreased to 94 ± 16 beats min. ($P < 0.001$) The jugular venous pressure was slightly raised in only one patient. Seven patients had a gallop rhythm still and six patients still had an apical systolic murmur No patient had a pleural effusion or ascites.

The cardiothoracic ratio had decreased to 0.57 ± 0.08 and only three patients had a ratio above 0.6 The electrocardiograms had changed little in three widespread T wave inversion had

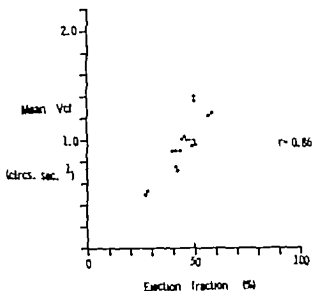


Fig. 3. Relationship of mean Vcf to ejection fraction, both derived from the echocardiogram. *Dotted lines* are the lower limits of the normal ranges.

been replaced by T wave inversion in the lateral chest leads only. The PCV had risen to 40 ± 6 per cent.

Echocardiograms (Table VI). The major changes were the reduction in the size of the chambers and the estimated cardiac output. There was no change in the indices of left ventricular function. The fall of the mitral valve diastolic closure rate from 13 ± 3 cm. sec. probably reflects the reduction of blood flow across the valve.

Systolic time intervals. (Table VI). There was little change: PEPI = 135 ± 18 msec., LVETI = 359 ± 21 msec., PEPI/LVETI = 0.4 ± 0.07.

Discussion

The accurate assessment of the performance of heart muscle is still difficult. As a pump the heart's product is cardiac output, but this is determined by the interaction of many factors such as myocardial contractility, aortic pressure (or afterload), degree of ventricular hypertrophy, and the magnitude of the venous return (or preload) which itself is affected by the peripheral vascular resistance, blood volume, and over-all vascular tone. To isolate the function of the muscle of the heart out of all these variables is almost impossible. However, certain pragmatic approaches are now recognized as being valid for defining groups. The ejection phase indices of left

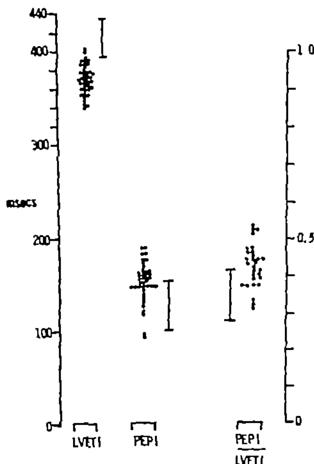


Fig. 4. Scattergram of the systolic time intervals for individual patients. *The vertical bars* represent the normal ranges.

ventricular function (mean velocity of circumferential fiber velocity (Vcf), ejection fraction, and fractional shortening) have been shown to distinguish between groups of patients with normal and abnormal left ventricular function. An important advantage is that they can be calculated from echocardiograms. The calculation of volumes from the left ventricular dimensions measured by echocardiography is more debatable. It was clearly recognized in this study that the individual values for any volume were only an approximatation. However, for studying groups of patients this method is sufficiently accurate to decide whether the stroke volume is very low, normal, or very high. Support for this comes from the results using the thermodilution technique for the measurement of cardiac output. The differences were not great in those individuals whose cardiac outputs were measured by both techniques.

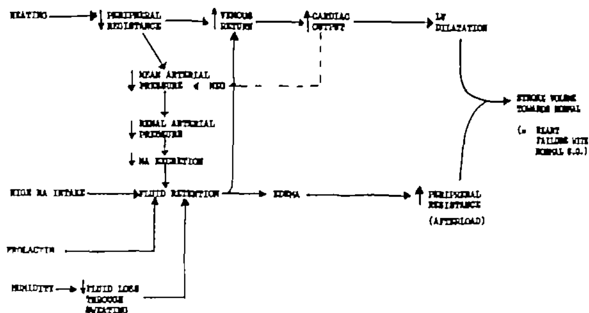


Fig. 5 Outline of the proposed mechanism to explain PPCF in Zaria.

Table IV Cardiac catheterization data

Patient	Mean RA (mm. Hg)	RV (mm. Hg)	PA (mm. Hg)	Cardiac output (liters min.)	HR (beats min.)	SV [illegible]
1	14	53/19	53/35	4.8 ± 0.49 (3)	110	[illegible]
2	13	55/17	55/36	7.0 ± 0.59 (9)	78	[illegible]
3	11	53/10	53/30	5.8 ± 0.69 (3)	130	[illegible]
4 ( )	20	50/22	50/37	4.7 ± 0.3 (5)	125	[illegible]
( )	13	45/15	45/30	5.2 ± 0.4 (8)	105	[illegible]
5	13	35/5-20	35/10-20	6.3 ± 0.46 (4)	140	[illegible]
6 (i)	10	45/10	–	6.2 ± 0.9 (9)	100	[illegible]
(ii)	8	25/9	25/15	5.2 ± 0.5 (6)	102	[illegible]
7	20	60/17	60/32	–	–	
8	13	52/10	52/33	–	–	–
9	18	60/18	60/35	–	–	
10	13	25/13	25/19	–	–	
Normal range	−1 +5	15-28/0-8	15-28/5-16	3.5-6.0		60-1[illegible]

RA = right trial pressure RV = right ventricular pressure; HR = heart rate; SV = stroke volume; PCW = pulmonary capillary wedge pre[illegible]
Figures in brackets are the number of determinations for which the thermodilution curves were satisfactory
— from "The Heart" ed by J Willis Hurst, 1974, p 83

The surprising fact that emerged from this study was that, despite the clinical evidence of advanced circulatory congestion and edema which was present in all the patients studied most had maintained relatively good left ventricular function and the cardiac output was high. By contrast, the two patients who had very low values for the mean Vcf and ejection fraction were the only two patients who had continuing signs of heart failure, similar to the pattern described in patients with a congestive cardiomyopathy In the remainder the cli[illegible] course and echocardiographic findings wer[illegible] like congestive cardiomyopathy Instead, hemodynamic findings were very similar to th[illegible] seen in patients with acute glumerulonephrit[illegible] although none of our patients had any eviden[illegible] renal disease. PPCF in Zaria, therefore, may b[illegible] example of congestion of the circulatory sys[illegible] which simulates congestive heart failure, which is not primarily due to it.

But why should apparently normal postp[illegible]

Table V Combined echocardiographic and thermodilution measurements

Patient no.	*Echo data* LVEDD (cm.)	E.F (%)	S.V (ml.)	C.O. (liters min.)	Thermodilution estimated C.O (liters min.)
1.	6.2	26	63	6.7	4.8 ± 0.49
2.	6 0	42	91	8.7	7.0 ± 0.59
5.	4 0	65	42	6.1	6.3 ± 0.46
6.	5 2	43	61	6.5	6.2 ± 0.9

LVEDD left ventricular end diastolic dimension, EF = ejection fraction, SV = stroke volume; C.O = cardiac output.

tum woman accumulate such large amounts of fluid? (Fig. 5) It has been suggested previously that the Hausa postpartum practices of eating food rich in salt and lying on heated mud beds may be responsible for overriding the normal control mechanisms of the extracellular volume.[illegible] The heating produces a low total peripheral resistance so that the mean arterial pressure cannot be raised except by increasing cardiac output. As the mean arterial pressure is the major determinant of urinary output,[illegible] this inability to raise the arterial pressure as efficiently as usual, in women already taking large amounts of sodium, inevitably leads to their retaining excess sodium and water In such postpartum women, prolactin, known to have sodium retaining properties, may also play a part. Fluid loss through sweating will also decrease as the humidity increases at the onset of the rains[illegible] (and this probably accounts for the peak of admissions at this time) The cardiac output will continue to rise in response to the increasing blood volume and venous return in an attempt to excrete the excessive fluid, until the reserves available from left ventricular dilatation and the Frank-Starling mechanism are fully used. This limit will vary for each individual and those with poor myocardial reserves, from whatever cause, will be unable to sustain the required cardiac output and will develop a form of high output failure. The combination of high venous pressures and a large blood volume rapidly produces gross edema (Fig. 5)

A further complication arises if the peripheral resistance should begin to increase. This is likely to happen once edema has formed because of a direct effect of edema on the vessels[illegible] and because the increased sodium content of a vessel wall

Table VI Follow up data (27 patients) (mean ± S.D)

Measurement	On admission	Convalescent
I Echocardiographic		
LVEDD (cm.)	5.8 ± 0.6	5.4 ± 0.7**
LVESD (cm.)	4.6 ± 0.7	4.2 ± 0.7
LA (cm.)	4.3 ± 0.6	3.2 ± 0.9*
Aortic root (cm.)	2.5 ± 0.2	2.5 ± 0.2
MV mean DCR (cm. sec.)	14 ± 5	9 ± 3*
Mean Vcf (circ. sec.)	1.2 ± 0.4	1.0 ± 0.3
Ejection fraction (%)	49 ± 12	50 ± 11
Fractional shortening	0.21 ± 0.07	0.2 ± 0.07
Estimated S.V (ml.)	99 ± 38	82 ± 35
Estimated C.O. (liters min.)	11.8 ± 4.8	7.5 ± 3.3*
2. Systolic time intervals		
LVETI (msec.)	3[illegible]3 ± 2[illegible]	359 ± 21
PEPI (msec.)	1[illegible]6 ± 22	125 ± 19
LVET/PEP	0.42 ± 0.07	0.4 ± 0.07

Significance of change from admission to convalescent. *p = < 0.1, **p = < 0.001

limits the ability of an arteriole to dilate.[illegible] Cooling will have the same effect. When the filling pressures of the left ventricle are high and the sarcomeres are fully extended, the stroke volume becomes very sensitive to change in afterload, dropping sharply with any further increase.[illegible] This will decrease the cardiac output back towards normal, thus exacerbating the situation even further The combination of a high inflow volume with an elevated peripheral resistance produces an elevation of the left ventricular work load far above that present in comparable high output states in which the mean arterial pressure is low It is possible that these combined loads are sufficient to produce myocardial damage, and this may account for the slightly poor left ventricular function seen in some of the patients. (Exactly the same event will occur on the right side of the heart if the pulmonary artery pressure rises) The fact that the women were able to cope with the hemodynamic load of pregnancy without any sign of heart failure suggests that they did not have pre-existing heart muscle disease.

The provoking factors of salt and heat are clearly important in explaining why PPCF is so common around Zaria. But the syndrome we see is similar to some of the previously reported cases. Thus, Demakis and colleagues[illegible] found that the chest radiograph became normal in 14 of 27 patients with PPCF and in these women the

prognosis was excellent with no further heart failure in 21 subsequent pregnancies. Johnson and associates reported a patient who was catheterized and in whom the cardiac output was normal and the hemodynamic data was interpreted as showing biventricular failure, probably of the high output type." Another study reported cardiac output results from ten patients. In seven patients the values were normal (3.6 to 6.1 liters/min) although the authors conclude that the "haemodynamic findings were characterised by low output biventricular failure." The other reports in the literature which contain cardiac output data are six case reports[illegible] (two were normal and four were low) and that of Pearce and co-workers,[illegible] who found that the cardiac outputs were low in three patients.

It is possible therefore that PPCF in temperate climates also may not be initially a primary myocardial problem. A more radical concept is that during the postpartum period the extracellular volume may expand more than is normally possible while the control systems are resetting after the pregnancy. Sodium retention and volume expansion may occur helped by the high prolactin levels. An expanding blood volume will, as above, produce an increasing venous return and although the mother is able to cope with this during the pregnancy she may only be able to do so if the peripheral resistance is low. However it may be that during the postpartum period in certain women the peripheral vessels respond to volume loads and excess sodium more vigorously. This rise in peripheral resistance may produce a small rise in the blood pressure. (It is possible that this is the mechanism of the well recognized postpartum rise in blood pressure seen in normal women.)[illegible] But more importantly this rise in the peripheral resistance will markedly increase the work load of an already dilated ventricle. Again as in our own patients, certain individuals may be incapable of coping with the combined demands of a high inflow volume and an increased after load, so that myocardial damage and a true cardiomyopathy may follow.

This theory reconciles two apparently conflicting views of the etiology of PPCF. Most authors have considered it to be a form of cardiomyopathy or intrinsic heart muscle disease. But as was pointed out by Brockington there are several objections to this concept. The major difficulty is that it does not explain the hypertension found in most cases, and it seems highly unlikely that any left ventricle that is already in failure due to a myocardial fault is able to maintain a higher than normal blood pressure. However although Brockington concludes that PPCF is hypertensive heart failure, he provides no plausible explanation for the fact that the presenting blood pressures are only moderately raised, they fall to normal quickly after treatment with diuretics, and the women do not need further treatment for hypertension. Therefore it seems reasonable to suggest that the primary event is volume overloading, which by dilating the ventricles makes them very sensitive to any increase in arterial pressure (which is also due to the same initial volume expansion). The consequent reduction of stroke volume in the face of a high venous return will accelerate the development of the symptoms and signs of congestive heart failure and possibly in a few result in permanent myocardial damage.

Therefore, although there are special predisposing factors in this area, the Hausa postpartum practices may be exposing a mechanism that is common to postpartum women throughout the world.

Summary

Ventricular function has been studied in [illegible] patients with the peripartum cardiac failure (PPCF) syndrome which occurs around Zaria. All patients had an echocardiogram on admission and 10 patients had right heart catheterization. Despite the gross edema, left ventricular function assessed by echocardiography and systolic time intervals was relatively good and the estimated cardiac outputs were high. At catheterization, although the pressures were high, the cardiac outputs were greater than normal in four out of six patients. No patient had a low cardiac output. These findings are not compatible with a severe heart muscle disorder or cardiomyopathy. We suggest that the primary event in PPCF of Zaria is fluid retention which leads to a form of high output cardiac failure. The postpartum practices in this area (taking high sodium diets and lying on heated beds) almost certainly cause the fluid to accumulate initially but the heart may be unable to meet the demands either because of pre-existing heart muscle disease or more likely because of a rise of the peripheral resistance due to the volume expansion, overburdens and dilated hearts and leads to myocardial damage.

Since there are similarities between this condition and PPCF in temperate climates, it is possible that there is a common mechanism which the traditional practices of this area have unveiled.

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Combined effects of graded hyperkalemia on activation and recovery

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The electrophysiological effects of potassium ion on the cardiac conduction system has been a subject of great interest to the physiologist as well as to the clinician for many years. Hering in 1907 first described cardiac arrest due to hyperkalemia In 1911 Mathison observed varying degrees of atrioventricular block in cats following potassium administration. Since then numerous studies have been conducted confirming the early observations, and with the aid of electrocardiograms various types of degrees of conduction abnormalities as well as arrhythmias have been described. An excellent review by Ettinger and associates has summarized the various effects hyperkalemia has on the cardiac conduction system along with correlation of the associated mechanical events, and intramural electrical activity

The purpose of this study was to establish the effect of titrated hyperkalemia in animals with carefully constrained normal electrolytes and blood gases. In addition to detailed observations of the effects at various concentrations of potassium on cardiac conduction tissue we wished to assess the quantitative relationships of the depolarization–repolarization process, to evaluate the effect of graded hyperkalemia on the ventricular gradient, and to evaluate possible mechanisms in the genesis of the sine wave.

Materials and methods

Ten mongrel dogs weighing between 12.15 and 17.1 kilograms were anesthetized with 30 mg of sodium pentobarbital per Kg. given intravenously, intubated, and were placed on a Harvard respirator set at a rate of 12 to 18 respirations per minute and a tidal volume of 200 to 250 ml of room air

A bipolar electrode was placed via right jugular vein high in the right atrium. Three tripolar electrode intracardiac catheters were inserted in the femoral vein and were passed retrograde into the right atrium and across the tricuspid valve to obtain His bundle recordings. A catheter was inserted via the femoral artery and was advanced into the central aorta for obtaining blood samples for oxygen saturation pH pO_2 pCO_2 and potassium, sodium, chloride, calcium and magnesium. Samples for these determinations were made in each animal at the beginning of the experiment, and every five minutes until termination of the experiment.

Electrocardiographic Leads II and V ... were recorded via subcutaneous needle ... with high speed techniques, as were His bundle electrograms and atrial electrograms (Fig. 1)

After obtaining a baseline electrical ... biochemical profile, a solution of potassium chloride (160 mEq per liter) in isotonic saline ... infused into a peripheral vein at a rate of 0... 0.98 mEq per minute. The animals ... constantly monitored by means of high fidelity ... high frequency recording onto AMPEX FR ...

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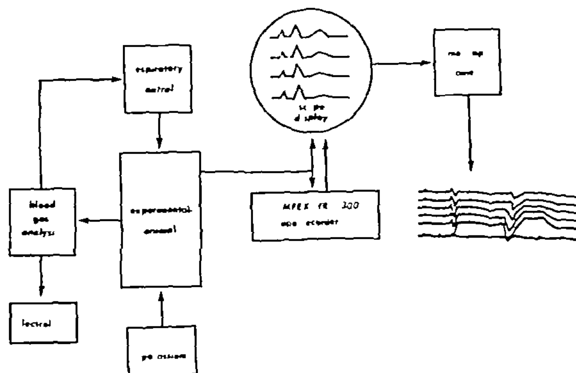


Fig. 1. A typical experimental setup.

magnetic tape for permanent storage with constant monitoring on a Tektronix oscilloscope. Final playback and recording onto permanent film was accomplished by means of a Grass Kymograph oscilloscopic camera at film speeds of 100 and 250 mm./second. The effective frequency response of the system was 0.2 to 3,000 Hz. Measurements were made of the total and fractionated PR intervals which included measuring the PA interval (the time lapse between the earliest atrial activity recorded from one of the surface leads and the A wave recorded from low right atrium), the A-H interval (the time lapse for the impulse to travel from the region of the low atrium through the atrioventricular node to the bundle of His) and the H-V interval (the time lapse for the impulse to travel from the bundle of His through the bundle branches and the Purkinje–myocardial junction). The Wilson ventricular gradient was extrapolated in each experiment by planimetering QRS and T areas of surface Lead II and was expressed as millivolts–milliseconds. Amplitude of the T wave, and duration of the QRS and $(QT - QRS)$ intervals were also measured in each animal at each concentration.

Results

A. Effect of potassium ion on A-V conduction systems. (Refer to Table I.) As the serum potassium (K+) level rose to a mean of 6.6 mEq. per liter the amplitude of the surface P wave and that of the intra-atrial P wave activity diminished, and at a mean K+ level of 9.03, the surface P wave activity disappeared. Atrial electrical activity however, as verified from the intra-atrial electrode, uniformly persisted till a higher serum potassium level. The loss of intracardiac evidence of atrial excitation was seen at a mean K+ level of 10.4. In one experiment atrial activity persisted, despite the absence of the His and ventricular activity (No. 7). In three experiments, an ectopic atrial rhythm prevailed before the cessation of the total atrial electrical activity.

Intra-atrial conduction time was prolonged at a mean K+ of 7.7 (range 6.1 to 9.0). A delay in A-V nodal transmission time occurred at a mean serum K+ value of 5.90 (range 3.2 to 6.8) and was progressive. His-Purkinje conduction delay occurred at a significantly higher potassium concentration, with a mean level of 8.34 (range 6.5 to 10.0). His bundle activity was recognizable as a discrete event always at higher K+ concentra-

Table I Concentrations of serum K+ (mEq per liter) at which various electrocardiographic changes occur

Experiment	Prolongation of PA interval	Prolongation of AH interval	Prolongation of HV interval	QRS duration	T ampl. increased	Loss of intra atrial P	Loss of His spike	CHB above the His	CHB below the His	AV dissociation	Sine wave	V fibrillation	Arrest
1	8.1	3.2	8.2	7.9	7.9	9.0	—	—	—	—	9.8	—	>1[illegible]
2	6.1	4.9	7.4	5.1	5.9	7.4	10.6	—	—	—	8.8	—	[illegible]
3	8.4	8.2	10.0	6.2	8.0	10.0	10.8	—	—	9.0	10.3	—	>[illegible]
4	6.5	5.6	8.6	5.6	8.6	12.8	> 13.4	—	—	9.9	< 13.4	> 13.4	
5	—	6.7	7.6	7.3	7.6	9.9	> 12.0	9.9	11.0	—	11 12.0	> 13.0	
6	9.0	6.3	8.2	6.3	6.7	10.0	10.2	—	10.0	—	11.[illegible]	—	>[illegible]
7	8.[illegible]	6.6	9.0	6.4	6.6	—	11.6	10.4	—		10.9	—	>[illegible]
8	7.2	6.[illegible]	9.8	6.4	6.8	12.0	13.0	—	—	11.0	12.6	—	[illegible]
9	6.7	6.2	9.0	5.7	6.2	11.5	15.2	—	11.4	9.0	> 13.0	—	>[illegible]
10	8.8	6.8	7.[illegible]	6.2	6.2	11.2	14.5	9.8	—	—	14.0	—	>[illegible]
Mean values	7.7	6.0	8.34	6.31	7.03	10.4	12.36				11.67		
± 1 SD	± 1.10	± 1.10	± 1.03	± 0.81	± 0.9	± 1.64	± 1.77				± 1.73		

* persistent His activity
* persistent atrial activity

tions than other areas of the conduction system (Fig. 2). In one animal (No. 1) His bundle excitation was seen to persist even after ventricular and atrial asystole. In another animal (No. 5) A V nodal Wenckebach was seen at K+ of 9.6 and H V Wenckebach at K+ of 10.8—before progressing to complete heart block below the bundle of His at K+ of 11.5 (see Fig. 3 and Table II).

B. Effects of potassium on depolarization and repolarization sequence. As is well known the QRS duration uniformly started widening with progressive hyperkalemia—mean K+ 6.31 (range 5.1 to 7.9). The quantitation of the progressive widening has not been described, however. As the serum potassium level rose to about three times the control value the basic ventricular excitation time doubled in each animal (72.5 ± 12.2 msec to 108 ± 21.6 msec). It was also noticed that the ventricular excitation sequence changed drastically with progressive hyperkalemia. At a mean K+ level of 7.0 (range 5.9 to 8.6) the T wave amplitude increased. However the ST T interval showed only a transient shortening (160.8 ± 21.1 msec. to 144 ± 16.4 msec.) followed by a progressive but very gradual prolongation with terminal rise (179 ± 36 msec.) (see Fig. 4). As hyperkalemia progressed above about 11.0 mEq per liter the QRS became too wide to measure. At this point the T wave amplitude increased further and finally resulted in the sine wave. In seven out of ten animals the His bundle activity was detectable at the sine wave stage with a [illegible] HV interval. This indicated that even at the sine wave stage, conduction still was via the His bundle and although excessively wide, the QRS did not reflect idioventricular rhythm.

C. Rhythm changes in hyperkalemia. With increased K+ level, junctional rhythm replaced sinus rhythm in nine out of ten animals (Fig. In three animals, as previously stated, an ectopic atrial rhythm preceded the onset of junctional rhythm. Junctional rhythm was due to one of the following mechanisms (Table III).

In one experiment a ventricular escape rhythm prevailed due to complete heart block below the level of the bundle of His and atrial asystole (Fig. 6). In two other experiments, a ventricular rhythm preceded the sine wave and was due to complete heart block below the level of the His bundle (Nos. 8 and 9). Ventricular fibrillation was seen as the terminal event in two experiments only (Nos. 4 and 5). All the other experiments had ventricular asystole as the terminal event.

Premature junctional complexes (PJC's), premature ventricular complexes (PVC's), and a short run of ventricular tachycardia was seen in one experiment only (No. 4).

D. Effect of hyperkalemia on ventricular gradient. As shown in Fig. 8, the ventricular gradient very gradually begins to diminish in [illegible]

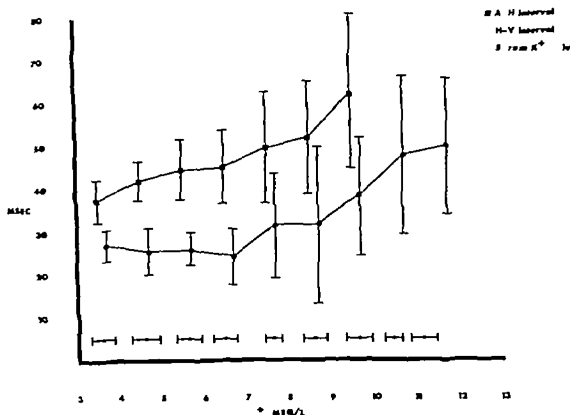


Fig. 2. Top tx curves represent the mean ± 1 standard deviation of A-H and H V intervals in msec. plotted along the ordinate against serum K + Mean serum potassium ± 1 standard deviation m milliequivalents per liter is plotted along the abscissa in the *lower part of the figure*

Table II Rhythm changes in Experiment 5

	Serum K+ in mEq /L	*Q-Q interval (msec.)*	*A-H interval (msec.)*	*H V interval (msec.)*	*QRS duration (msec.)*	*Rhythm*
A	4.4	332	38	26	52	Sinus rhythm
B	7.6	352	40	26	58	Ectopic atrial rhythm
C	9.5	408	–	44	87	A H Wenckebach
D	10.8	656	–	–	158	Junctional rhythm with H V Wenckebach
E	11.5	2008	–	–	194	Ventricular rhythm with complete heart block below the His bundle

range of 6 to 8 mEq /L. of serum K + abruptly so, with even higher potassium levels until finally they become negative as hyperkalemia progresses. The last value in the figure represents the ventricular gradient at the time of the sine wave.

E Relationship of other cations and arterial blood gases. In these animals Na + Ca + + and Mg + + did not fluctuate during the experiments, and thus in these circumstances the contribution to the observed electrocardiographic changes from these ions is probably minimal. Arterial gases, pH, and pCO stayed uniformly constant at lower K + levels, although almost always an alkalotic pH was seen at the time of the terminal event.

Discussion

Sinoventricular and intra-atrial conduction In 1886 McWilliam, and later Vassalle and coworkers[4] demonstrated the *existence of so-called* "sinoventricular conduction" in arrhythmias during potassium intoxication in a canine model.

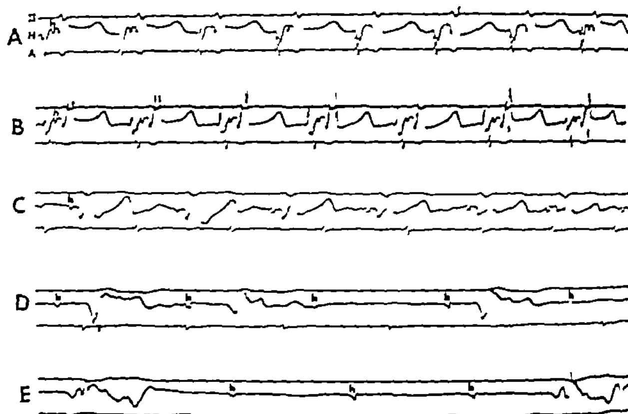


Fig. 3 Rhythm changes observed in Experiment 5 with progressive hyperkalemia, where A = high right atrial electrogram, H = His bundle electrogram, II = surface lead II. Time scale = 100 msec. See accompanying *Table III* for further explanation.

Table III Mechanisms for the genesis of junctional rhythm

A Atrial arrest	Junctional escape rhythm (No. 1)
B A-V dissociation	Accelerated junctional rhythm following atrial activity (Nos. [illegible])
C Complete A-V block above the level of the His bundle	Junctional rhythm (Nos. [illegible] 10)

Sano and associates have described similar phenomena in rabbit atria, showing the differential effect of potassium upon atrial muscle and specialized internodal conduction fibers. We were able to demonstrate persistent atrial activity as recorded by the intra-atrial electrogram, long after the disappearance of any discernible P wave on the surface electrocardiogram. In seven animals the polarity of these atrial P waves as seen on the high right atrial lead and that of the His bundle lead did not show any change from that recorded during normal sinus rhythm; loss of atrial activity or any change in the p[illegible] of the atrial signal (seen in three experimen[illegible] result in remarkable change in the [illegible] response. These results exclude as an expla[illegible] the concept of sinoventricular conduction [illegible] these particular circumstances.

A-V conduction. The first measurable de[illegible] the A-V conduction system was at the A-V [illegible] It was progressive with increasing levels of se[illegible] potassium. This culminated in complete A[illegible] block above the level of the bundle of His in [illegible] animals (Nos. 5, 7 and 10) with further ri[illegible] potassium levels, indicating that A-V no[illegible] probably the most sensitive portion of the spe[illegible] ized conduction system to hyperkalemia. C[illegible] versely, we uniformly demonstrated co[illegible] H-V intervals at the lower levels of hyperka[illegible] and prolongation was seen only at signific[illegible] higher potassium concentrations.

Persistent His bundle activity, tho[illegible] diminished amplitude, with no discernible [illegible]

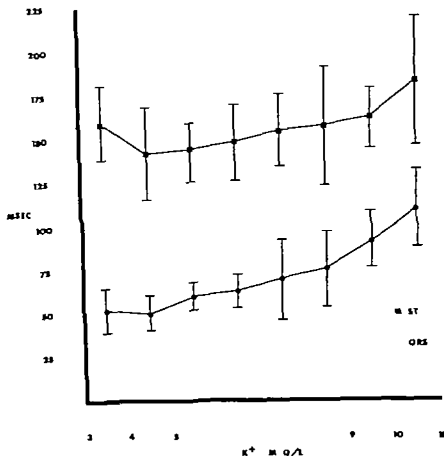


Fig. 4 Mean ±1 standard deviation values of QRS and ST T (QT-QRS) are plotted in msec. along the ordinate against serum K+ in mEq /L.

ing of the His spike until the stage of the sine wave, *together with a constant* H V interval, suggest that His bundle is the least sensitive conduction system structure to hyperkalemia.

Added support to this concept was the single experiment (No. 1) in which the His bundle activity persisted even in the face of both atrial and ventricular asystole—these circumstances suggested complete exit blockade somewhere between the His bundle and its branches and the distal Purkinje myocardial junction. Demonstration of complete blockade below the His level in three other experiments (Nos. 6, 8, and 9) with persisting His activity also contribute to this concept.

Rhythm and ventricular gradient. Rhythm changes in hyperkalemia have been well established by Pick[1] and by Trautwein.[11] The postulated mechanisms are: (a) reentry and (b) acceleration of the subsidiary pacemaker due to slowing of the primary pacemaker In our experiments an *escape mechanism* was another (though similar) mechanism due to complete failure of the higher pacemaker

Fig. 7 depicts the diagrammatic representation of the normal membrane action potentials of endocardium and epicardium and of those during graded hyperkalemia. As shown in the left panel, the epicardial action potential starts later but terminates earlier than the endocardial action potential. This information, when integrated throughout the heart and translated to the surface ECG manifests itself as the QRS and T wave, (as shown in the shaded area). This differential rate of recovery between the endocardial and the epicardial action potentials results in an electrical gradient, termed the ventricular gradient by Wilson and associates. This gradient is perceived on the surface ECG as the algebraic sum of the areas of QRS and T wave. With

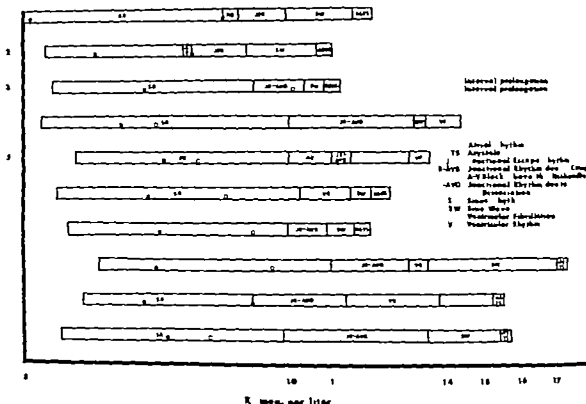


Fig. 5 A bar diagram of the rhythm changes in each experiment plotted (Nos. 1 to 10) with progressive hyperkalemia. Levels of serum K + at which A-H and H-V interval prolongation was noticed is also shown for each experiment

progressive hyperkalemia the basic ventricular excitation time and T wave amplitude is increased The middle panel depicts the membrane action potentials during the stage of the peaked T waves. Though the duration of the action potential, the plateau phase and the overshoot are decreased and the resting membrane potential is diminished, the ventricular gradient is changed very little

The right panel of Fig. 4 shows action potentials at significantly higher K + concentrations, which demonstrates the greater separation of endocardial and epicardial excitation, indicating slowing of conduction within the ventricles. The abbreviated repolarization (affecting to a relatively greater extent the inherently longer endocardial phase 2 and 3) may be translated in an intact myocardium into increased temporal symmetry between the membrane action potentials of endocardium and epicardium ultimately contributing to the disappearance of the gradient. Repolarization is now solely dictated by the order of depolarization, and no longer influenced by the differential between the action potentials of endocardium and epicardium, resulting in an opposite polarity for QRS and T This phase difference between QRS and T coupled with the distal Purkinje blockade, further causes the duration of excitation to approximate the duration of the recovery resulting in the sine wave.

Hypoxia, hyponatremia, and hypocalcemia have been shown to contribute to the observed ECG changes of hyperkalemia—including arrhythmias and conduction disturbances.

In all but two of our experimental animals, the terminal event was electrical asystole, with cessation of His bundle activity—probably the final sequel to progressive decrease in resting membrane potential. Two experiments showed ventricular fibrillation as the terminal event, probably due to the focal reentry mechanism.

Summary

We have demonstrated the progressive transmission delay in the A V conduction system in graded hyperkalemia against a background of otherwise normal cations, and known blood gas relationships. This extends and further quan-

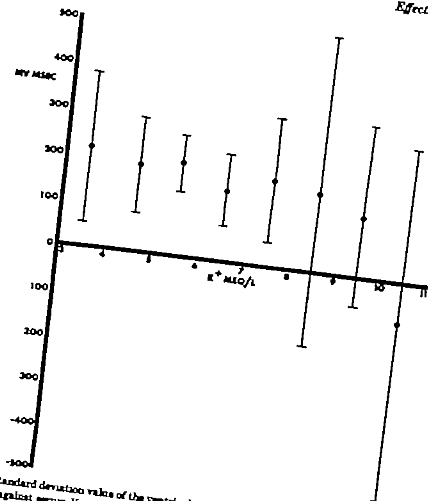


Fig. 6. Mean ±1 standard deviation value of the ventricular gradient expressed as millivolts-milliseconds plotted along the ordinate against serum K+



Fig. 7. Diagrammatic representation of membrane action potentials of epicardium and endocardium during normokalemia and graded hyperkalemia with shaded areas representing QRS and T

tates the work of others. We were unable to demonstrate sinoventricular conduction, as atrial activity was consistently recordable when surface P waves disappeared. The His bundle appears to be the least susceptible conduction system structure to hyperkalemia. Finally we have postulated the possible mechanism for the genesis of the sine wave including loss of electrical gradient with resulting phase difference of QRS and T associated with maintenance of His bundle activity with progressive, distal, Purkinje blockade.

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Case reports

Aortocoronary sinus anastomosis A postoperative follow up 24 years later*

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Currently revascularization of the heart utilizes procedures involving direct systemic–coronary arterial anastomosis. Although other methods of revascularization have been introduced, debate concerning their validity has limited their clinical use. One such procedure, popularized by Beck, arterialized the coronary sinus attempting to oxygenate the myocardium distal to significant coronary artery obstruction. Variations of this procedure have recently received renewed attention[1-4, 12, 17, 18] and prompted us to describe our experience with a long term survivor of the Beck II operation.

Case report

M. P was first evaluated for frequent, typical angina pectoris in 1949 at age 37. In 1951, an uncomplicated myocardial infarction occurred with characteristic electrocardiographic and enzyme changes. Because of progressively disabling angina over the next two years, Beck II procedure was performed in two stages, 1953 to 1954. His postoperative course was uncomplicated and he had no complaints suggestive of angina or equivalents during periodic evaluations over the next eleven years. A heart murmur was never noted.

In 1965, he was hospitalized after several weeks of fever exertional dyspnea, fatigue and edema, with Streptococcus viridans endocarditis involving the aortic valve. An excellent response resulted with penicillin therapy and he became totally asymptomatic. In June 1966, exertional and paroxysmal nocturnal dyspnea prompted readmission. Evidence for mitral and aortic insufficiency was then present, blood cultures were sterile, and digoxin and diuretics ameliorated most of his symptoms. Over the next year, he again began having infrequent episodes of typical effort angina relieved by nitroglycerin and on December 23, 1967 he had an acute, uncomplicated, anterior myocardial infarction.

In 1968, catheterization studies revealed elevated right and left heart filling pressures, diminished effective cardiac output, and small left-to-right shunt at the atrial level (see Table I). No pressure gradients were present and the aortic pulse pressure was widened. Left ventriculography revealed generalized reduction in wall motion and no comment was made relative to mitral regurgitation. Aortography showed 2+ aortic insufficiency. *Selective coronary angiography* documented total occlusion of the proximal, non-dominant right coronary and 80 per cent narrowing of the proximal anterior descending branch of the left coronary. The circumflex system had "lumen outline irregularity" without significant localized narrowing. A thoracic aortogram revealed widely patent communication between the descending thoracic aorta and coronary sinus as the coronary venous system was well visualized with "retrograde shunting" from the sinus to the right atrium (Fig. 1).

Digitalis and diuretic treatment continued,
was added for frequent PVC and 5 to
per day were required for angina.
Class III) for almost five years until he was ... on
August 5, 197[illegible], with acute pulmonary
fibrillation with rapid ventricular
digoxin and furosemide controlled these ... three
days later refractory
occurred.

At postmortem, the heart weighed
markedly dilated and thickened
sinus and great
shunt ... The right atrial ...
atrial

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Fig. 1 Thoracic aortogram revealing widely patent communication between descending thoracic aorta and coronary sinus.



Fig. 2. Dilated coronary sinus and patent shunt. 2 = aorta. No. 3 = patent aortocoronary sinus shunt. 4 = dilated coronary sinus. No. 5 = dilated coronary v

left trium and entricle were markedl dilated and thickened. The tricuspid and pulmonic valves appeared normal, but mitral valve orifice measured 10 cm in diameter with some leaflet opacification and thickening, but no egetations. There was also some thickening of the chordae tendinae. The aortic valv was 7 cm. in diameter with rolled, thickened cusps and small perforations of the non-coronary leaflet with calcification. The entricular septum was markedly thickened and patchy fibrosis occurred throughout the left ventricular myocardium with no evidence of aneurysm or recent infarction. The origin of the left main coronary was significantly (>75 per cent) narrowed with plaque significantly occluding its proximal anterior descending branch. The right coronary was totally occluded proximally and recannalized. N comment was made about significant narrowing in the circumflex coronary system. The major coronary eins were arterialized with marked intimal and medial thickening and plaque formation. Multiple areas of calcification were present through both the coronary enous and arterial systems. The aorta revealed marked atheromatous changes, particularly t the area of a graft to the coronary sinus

Discussion

Pratt[4] first proposed in 1898 utilizing the coronary veins as a route to oxygenate the myocardium. Bakst and colleagues reported improving mortality following major coronary artery ligations in dogs, after arterializing the coronary sinus. Beck and co-workers[4] confirmed t observations in more extensive studies in l These results prompted Beck to apply concept to coronary artery disease patients procedure, however declined in popul because of the multistage surgery required, the high operative mortality rate (29 per c associated with it. In 1956, Blanco and associates[14] used retrograde coronary sinus perfu for myocardial protection during aortic c clamping to permit aortic valve visualiza Similarly Lillehei and co-workers also rep the use of this technique in a patient with s calcific aortic stenosis. Later studies from same group in animals and further clinical suggested that retrograde sinus perfusion di appear unreasonable.[13]

However clinical interest in the use of technique waned as the use of pump oxygen for cardiopulmonary bypass increased a selective coronary artery perfusion and hyp mia were introduced for myocardial p tion.

Despite a reported improvement in mor with the Beck II method use of the proc

Table I Cardiac catheterization data

		O_2 content	Saturation	Pressure
	SVC	14.3	63.19	
	IVC	16.0	70.43	—
(Hi)	RA	14.9	65.74	10
(Mid)	RA	17.7	71.49	
(Low)	RA	17.0	73.02	
(Tri)	RV	1 .9	76.96	60/10-12 (p wa)
(Mid)	RV	17.7	78.09	
(Oft)	RV	17.6	77.82	
	MPA	18.0	79.47	80/22 (45)
	RPA	18.1	79.99	
	LPA	17.7	78.19	
	Ao	21.6	95.09	120/52 (75)
(PAW)	PVC			(22)
	LV			120/22
	BA			140/65 (87)
	CO/CI	4.2 L./min. 2.1 L./min./M.		
SBF/PBF		4.3 L./min. 8.2 L./min./M.		
L R shunt 4.3 L./min.				
PBF/SBF		1.8:1		
HR 70 BPM				

has been discontinued with the development of the more logical and successful coronary artery bypass procedure by Favaloro[13] and by Effler and colleagues.[14]

Renewed attention to retrograde venous perfusion was prompted by several recent observations. Conclusive studies demonstrated a lack of venous congestion or an increase in left ventricular size during partial coronary sinus closure.[16] The use of myocardial scanning, intramyocardial ECG and PO measurements, and myocardial force measurements confirmed earlier speculation purporting to effectively perfuse and oxygenate the myocardium by utilizing the coronary venous system. Reattention to the use of coronary veins for definitive surgery in patients with coronary disease has also appeared.[12-17] These considerations prompted the case report described here.

It is open to speculation whether the patent aortocoronary sinus anastomosis actually resulted in improved myocardial oxygenation in our patient. The clinical record indicates, however that he was considerably improved relative to relief of symptoms relating to myocardial ischemia for a very long period postoperatively In fact, it appears that while he had become clearly Class III preoperatively he was Class I after surgery in 1954. In addition, he clearly tolerated the hemodynamic burden of the volume overload related to the aortic and mitral incompetence and the left to-right shunt for over 10 years despite severe coronary artery disease.

Histologic evidence of the long term patency of this type of shunt in patients and the ability of the coronary veins to arterialize and develop atherosclerotic changes has not been described, to *our knowledge. Interestingly the patient's death* was a direct result of complications associated with the presence of a long term shunt. Nevertheless, it would appear that in selected patients, perhaps those with severe multiple disease with poor distal run-off and severe symptoms, a procedure such as that described in our report might be considered. In our patient it would appear that the potentially high surgical morbidity was outweighed by the long benefit manifest by relief of angina, and adequate myocardial function. Enthusiasm must be tempered, however since *the necessary left to-right shunt added to the* volume overload and probably provided the nidus for bacterial endocarditis in our patient. In addition, of course, we do not know the angiographic status of the coronary arteries in our patient at the time of surgery Conceivably venous stasis or occlusion could have caused myocardial infarction and/or subsequent accelerated coronary atherosclerosis.

Our report may raise more questions than it answers. Perhaps the concept of retrograde perfusion of the myocardium is a viable alternative to direct revascularization, and myocardial preservation during surgery is another possible application of this technique. Further studies might be able to provide answers to these important questions. These additional considerations not apparent from early reports related to this procedure, must be approached if such a technique is to be revived.

Summary

Historically attempts to increase myocardial blood flow surgically have had mixed results. This report describes the long-term follow-up of a patient with the Beck II procedure, who apparently was significantly improved by this method of retrograde coronary sinus perfusion.

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Flutter of the mitral valve associated with a diastolic murmur in the absence of disease

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Although the echocardiographic finding of mitral leaflet flutter is being recognized increasingly in settings other than aortic insufficiency, this observation is rarely noted in normal patients. Similarly, diastolic murmurs are seldom appreciated in patients without cardiac disease. This case report describes a patient with physical and phonocardiographic findings of a mid-diastolic murmur, echocardiographic findings of mitral leaflet flutter, and a normal cardiac catheterization and angiographic study. The presence of both an innocent diastolic murmur and the echocardiographic finding of mitral leaflet flutter has not been documented previously in the literature.

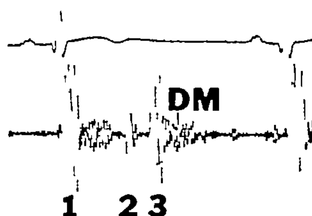


Fig. 1. Phonocardiogram shows the low frequency third heart sound immediately followed by the low frequency diastolic murmur. Also recorded is the systolic ejection murmur. The tracing was recorded at the apex at 50 Hz.

Case report

A 17-year-old man, previously asymptomatic, was admitted with a one-day history of exertional hemoptysis. There was no prior history of congenital heart disease, endocarditis, or rheumatic fever.

Physical examination revealed a well-developed muscular man with a blood pressure of 120/62 mm. Hg and a regular pulse of 68/minute. The point of maximum cardiac impulse was not displaced. There were no thrills, lifts, or heaves. The first heart sound was normal. The second heart sound was physiologically split. A loud third heart sound was immediately followed by a short, grade II/VI, low-pitched diastolic murmur at the apex (Fig. 1). A Grade II/VI systolic ejection murmur was heard along the left sternal border with radiation into the left carotid artery.

The electrocardiogram demonstrated sinus bradycardia and non-specific ST-T wave changes. The chest x-ray was normal. An echocardiogram revealed marked, fine diastolic fluttering of the mitral leaflets (Fig. 2). There was an increased left atrial to aortic root ratio with a small aortic root (18 mm.) and normal-sized left atrium (34 mm.).

Fiberoptic bronchoscopy showed mild hyperemia in a right upper lobe segment which was presumed to be the basis for the patient's hemoptysis. The remainder of the pulmonary evaluation was unremarkable.

Right and left heart catheterization revealed normal pressures and flows. No intracardiac shunts or valvular gradients were detected. The aortic root angiogram in the left anterior oblique projection demonstrated a small aortic root with no

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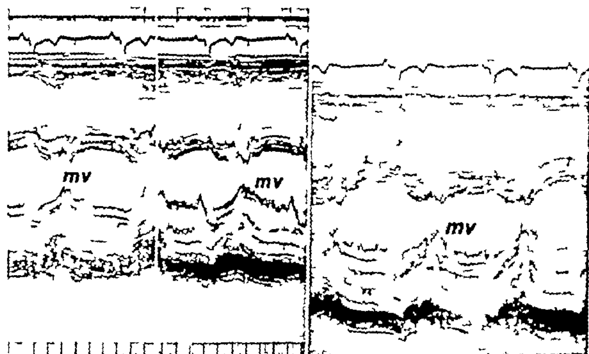


Fig. 2 Echocardiogram shows fine diastolic fluttering of both the anterior and posterior leaflets of the mitral valve

aortic regurgitation. The left ventriculogram demonstrated normal wall motion and ejection phase indices with no mitral regurgitation. Mitral valve leaflet fl[illegible]ering was observed in the left anterior oblique projection of the left ventriculogram.

Discussion

In 1966 the association of echocardiographically determined mitral leaflet flutter with aortic regurgitation was first made by Joyner and associates. Winsberg and colleagues regarded mitral valve flutter as a highly specific finding for aortic regurgitation. In their study 500 controls had no mitral valve flutter whereas 11 of 35 patients with clinical aortic regurgitation had unequivocal mitral valve flutter. They discriminated between the low frequency vibrations of the anterior leaflet in patients with atrial fibrillation (5 to 10 Hz) and the more rapid vibrations in aortic regurgitation (30 to 40 Hz). The mechanism of mitral valve flutter in patients with aortic regurgitation is thought to be due to impingement of two streams of flow on the mitral valve: the regurgitant blood from the leaking aortic valve and the emptying of the left atrium, both striking a suspended anterior leaflet causing it to vibrate.

The presence of mitral valve flutter in patients without aortic regurgitation was noted by Meyer and co-workers[3] in tetralogy of Fallot, ventricular septal defect with and w[illegible] pulmonary band, pulmonary hypertension, pulmonic stenosis. They observed mitral [illegible] flutter in about three-fourths of the patients [illegible] tetralogy of Fallot or combined ventricular [illegible] defect and right ventricular outflow obstru[illegible] and in about one-third of those with [illegible] ventricular septal defect. The oscillations [illegible] mitral valve in ventricular septal defect [illegible] typically more indistinct than in aortic regur[illegible]tion. They found no mitral valve flutt[illegible] patients with isolated mitral regurgitation [illegible] patent ductus arteriosus. Later however inv[illegible]gators noted that mitral flutter may be prese[illegible] isolated mitral regurgitation.[illegible] Coarse, b[illegible] flutter of the mitral leaflets is thought to occ[illegible] mitral regurgitation secondary to general[illegible] myocardial dysfunction or regional left ventri[illegible]lar dysfunction involving the base of the papil[illegible] muscle. Left ventricular dilatation is usu[illegible] present in conditions associated with flutter [illegible] the mitral valve.

Two specific patterns of mitral leaflet flu[illegible] were recently reported in association with a [illegible] mitral leaflet: early diastolic flutter of the po[illegible]rior mitral leaflet and coarse diastolic flutt[illegible] the anterior leaflet. The flutter of the ant[illegible]

leaflet is usually of greater amplitude in aortic regurgitation, whereas posterior leaflet flutter may be more prominent in other conditions associated with mitral valve flutter.

Flutter of the mitral leaflets has been described in patients with d-transposition of the great vessels who subsequently underwent Mustard repair. The mechanism postulated was the relatively restricted atrial tunnel resulting in turbulent blood flow across the mitral valve. Minimal electronic noise in sensitive echocardiographic recorders can produce vibrations resembling flutter. However, these are seen throughout the cardiac cycle, rather than being confined to diastole.

A diastolic murmur in a patient with isolated severe aortic regurgitation was first described in 1862 by Austin Flint and bears his name. He postulated that the regurgitant blood caused early filling of the left ventricle and hence, early coaptation of the mitral leaflets before atrial contraction. *Subsequent atrial contraction forced* blood through the coapted mitral leaflets which throws them into vibration and gives rise to the characteristic blubbering murmur."[1] Of course diastolic murmurs are heard in organic mitral stenosis. However diastolic murmurs have been reported in many settings other than aortic regurgitation or organic mitral stenosis.

Weinstein and Lev[4] described the occurrence of apical diastolic murmurs in patients with enlarged hearts without mitral stenosis. The common features in their series included marked dilatation of all chambers of the heart and an abnormal myocardium. They theorized that in the presence of dilated heart chambers an apical diastolic murmur could be heard without any associated aortic regurgitation or mitral stenosis due to the "relative mitral stenosis" produced by the dilated left atrium and left ventricle. Luisada and Montes[1] recorded diastolic murmurs by phonocardiography in patients with a large left *atrium, normal mitral orifice*, and a very large left ventricle. They speculated that two factors, increased flow and the disproportion between the normal mitral orifice and the large left heart chambers, especially the left ventricle, produced the murmurs. All of their patients with diastolic murmurs had some form of organic heart disease.

Apical diastolic murmurs resembling the murmur of mitral stenosis were found in a large portion of cases of patent ductus arteriosus. Three factors were regarded as important in their production, an enlarged left ventricle, the presence of the shunt causing increased blood flow through the left side of the heart, and the increased flow through the mitral valve.[13] Ravin and Darley[13] hypothesized that diastolic murmurs were common in children because of thinner chest walls and thinner ventricular musculature.

High-pitched diamond-shaped diastolic murmurs have been recorded by intracavitary phonocardiography in normal children. Similar murmurs have been detected in patients with large left-to-right shunts and normal atrioventricular valves, severe anemia, systemic hypertension, and rheumatic, coronary or congenital heart diseases.[14] In contrast to these high pitched murmurs, mitral flow murmurs are expected to be of low (as in our case) rather than of high frequency. Luisada and Dayem[15] noted that inaudible *low frequency diastolic apical vibrations* can sometimes be recorded phonographically in normal young adults. These oscillations may increase in a hyperactive cardiovascular system, as seen with exercise or the hyperkinetic syndrome. Luisada and Dayem[15] postulated that the origin of these vibrations was from the distension of the left ventricular wall, since they frequently begin with a loud third heart sound and represent after vibrations of this sound.

Our patient demonstrated the unique combination of a benign, low-pitched diastolic murmur auscultated on physical examination and recorded by external phonocardiography in association with fine mitral leaflet vibrations seen on echocardiography and left ventriculography in the absence of disease. The mechanism of the murmur production is uncertain, but on review of the literature, two basic theories have been suggested. The first is the concept of "relative mitral stenosis" with a normal mitral valve in the presence of an enlarged left ventricle. However our patient had a normal-sized left ventricle. Since the aortic valve size was in the lower range of normal, the mitral valve may also have been "relatively" small in a patient with a normal-*sized left ventricle. Thus* "relative mitral stenosis" may have been the cause of his murmur. A second theory that must be considered is that these murmurs arise from left ventricular wall distension during diastole and are produced by

vibrations following a loud third heart sound. That these vibrations could include the mitral leaflets or at least the mitral valve apparatus and be manifested as flutter on echocardiography and ventriculography is possible, but unproven.

Summary

A patient is presented with the unique combination of a low pitched apical diastolic murmur auscultated on physical examination and corroborated by external phonocardiography in association with the echocardiographic and ventriculographic findings of mitral leaflet flutter in the absence of disease. This has not been documented previously in the literature. Possible mechanisms for the production of the diastolic murmur and mitral valve flutter are discussed.

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Atrial myxomas A fifty year review

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Cardiac myxomas have been recognized as a distinct morphologic entity for over 200 years. One of the first reviews appearing in the English literature was by Yater in 1931, who reported two myxomas and reviewed the 75 myxomas which had been previously reported. Up until 1950 however it was believed that tumors of the heart were exclusively an autopsy diagnosis. With the advent of cardiac catheterization and cardiac surgery however for the first time tumors of the heart could be diagnosed clinically In 1951 intracardiac myxoma was recognized by angiography and in 1954 the first atrial myxoma was excised using cardiopulmonary bypass. Since that time there has been a vast increase in the number of clinical reports on the diagnosis and treatment of left atrial myxomas.[1-4] Over the past five years, however an additional major step has been made in the clinical recognition of atrial myxoma with the advent of noninvasive procedures which likely provide even greater ease and sensitivity in clinical detection of these tumors.[5-18]

In this review we report findings on the 24 consecutive atrial myxomas that have been seen at The Johns Hopkins Hospital, either at autopsy or operation, since the first in 1928. These patients illustrate the changes that have occurred in the clinical presentation and diagnosis of myxomas in the recent past.

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Features of 24 patients with atrial myxomas *presenting over a 50 year period*

The clinical features of the 24 consecutive patients with atrial myxomas diagnosed at The Johns Hopkins Hospital since 1927 are summarized in Tables I and II. The patients were all adults, ranging in age from 24 to 74 years, and 71 per cent of them were women. Of the 24 myxomas, 22 (92 per cent) were in the left atrium 12 (50 per cent) were diagnosed during life and came to operation. Clinical signs and symptoms included recent onset congestive heart failure in 13 patients, chest pain in seven patients, episodic pulmonary edema in four patients, and precordial systolic murmurs in 12 and murmurs of mitral stenosis in nine patients. In five patients, there was clinical evidence of systemic embolism including a cerebrovascular accident in four and femoral artery embolism in one. Of the 24 patients, 21 were in normal sinus rhythm, one was in chronic atrial fibrillation, and two had paroxysmal atrial fibrillation. Duration of symptoms of cardiac dysfunction ranged from 2 to 84 months, with an average of 15 months. In four patients there were no signs or symptoms of their left atrial myxoma by retrospective review of the clinical charts, whether or not the myxoma was diagnosed.

In half of the patients reviewed the diagnosis of cardiac myxoma was made during life (Table III) In six patients the diagnosis was made at the time of cardiac catheterization, and in five of the six patients it was a surprise catheterization. In three of four patients in whom echocardiograms were performed (Fig. 1) the myxoma was detected. In the fourth patient the echocardiogram was technically poor and did not suggest a myxoma, but did suggest that the mitral valve was normal. In two patients the diagnosis was a surprise finding

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Table I Cardiac myxomas. 50 year consecutive series from The Johns Hopkins Hospital

Number of patients	24
Age (years)	50 ± 12
Sex	17 F (71%)
Location of myxomas	
Right atrium	2
Left atrium	22
Duration of symptoms (months)	15 ± 22 (2-84)
Number diagnosed in life	12 (50%)
Number operated upon	12 (50%)
Number dying from myxomas	10 (42%)
Before 1960	9
Since 1960	1
Causes of myxoma deaths	
Sudden death	5
Congestive heart failure	3
Postoperative complications	2

Table II Myxomas: Clinical signs and symptoms

Congestive heart failure	13 (54%)	
Mitral stenosis murmur	9 (38%)	
Chest pain	7 (29%)	
Pulmonary edema	6 (25%)	
Embolism	(21%)	
CVA		4
Femoral artery		1
Electrocardiogram		
Normal sinus rhythm	21	
Paroxysmal atrial fibrillation	2	
Chronic atrial fibrillation	1	

Table III Cardiac myxomas: Clinical diagnosis in 24 patients

Diagnosis made during life	12 (50%)
At operation	2
At catheterization	6
By echocardiogram	3
By femoral embolus	1
Number not diagnosed	
Before 1960	9/11 (82%)
After 1960	3/13 (23%)

Table IV Left atrial myxomas: Simulators of disease

1. Mitral stenosis
2. Collagen vascular disease
3. Infective endocarditis
4. Idiopathic paroxysmal atrial fibrillation
5. Myocarditis

at the time of operation, and in one patient the diagnosis was made from histologic examination of a femoral embolus. In this study there were 11 patients with cardiac myxomas prior to 1960, and in nine or 82 per cent of them, the diagnosis was not made during life. Of the 13 patients that have been studied since 1960, the diagnosis was not made before death in only three of them. Of the patients in whom the diagnosis was not made in the recent group, two had no clinical symptoms by retrospective review of the chart. Noninvasive studies on patients with left atrial myxomas included a nuclear angiocardiogram in one patient, a one-dimensional echocardiogram in four patients, and a two-dimensional echocardiogram in two patients. These noninvasive diagnostic techniques were the primary method of diagnosis for three of the four patients, and one of these three latter patients went directly to operation without cardiac catheterization.

As they are well known to do, the atrial myxomas simulated both cardiac and noncardiac disease (Table IV). In nine (38 per cent) patients rheumatic mitral stenosis with or without mitral regurgitation was diagnosed, in three patients collagen vascular disease was suspected leading to steroid therapy in one. In two patients infective endocarditis was thought to be present, and in one, idiopathic tachyarrhythmia, and in one myocarditis were the leading diagnoses. Both of the patients with right atrial myxomas presented with right-sided congestive heart failure of unknown etiology which led to cardiac catheterization and diagnosis in one of them.

Of the 24 patients with atrial myxomas, 14 have died, and 10 of the 14 deaths were attributable to the atrial lesion: five died suddenly without other explanation, three died of intractable heart failure and two died after operation for removal of the myxoma. Nine of these 10 patients dying because of atrial myxomas died before 1961.

At autopsy or surgery all 24 myxomas were located in the atrial cavity (right in two, left in 22) attached to the atrial septum in the region of the fossa ovalis (Fig. 2). The masses ranged in size from 1 to 8 cm. (average 4.9 ± 1.9 cm.) in widest diameter and 75 percent were pedunculated. There appeared to be a general correlation between the size or presence of a pedicle and clinical signs or symptoms. The mean maximum diameter of the 12 myxomas not diagnosed during life was 3.9 ± 1.8 cm. and of the four myxomas



Fig. 1 Echocardiogram from one study patient showing the cloud of echoes in the mitral orifice behind the anterior leaflet of the mitral valve (MV) which are characteristic of left atrial myxomas. RV = right ventricle.



Fig. 2. Heart which has been sectioned transversely through both left (LA) and right atria (RA) viewed from above, showing myxoma residing within the left atria attached to the inter atrial septum (IAS). A = aorta, PA = pulmonary artery

unassociated with any clinical signs or symptoms was 3.2 ± 1.7 cm. The myxomas had smooth, polypial surfaces and all histologically showed abundant amorphous interstitial ground substance scattered with undifferentiated mesenchymal cells and double-walled blood vessels (Fig. 3)

Myxomas in perspective

Myxomas are believed to be the most common primary tumor of the heart. These lesions almost always occur in the atrium and frequently present as simulators of both cardiac and noncardiac disease. Despite a great deal of interest in atrial myxomas, most information currently available is based on isolated case reports or small collected series of less than five or 10 patients. In part this is due to the relative rarity of this lesion. In our own institution, the autopsy incidence of atrial myxomas is 0.03 per cent, a figure similar to that reported by others. With the advent of improved diagnostic methods and surgical intervention, however experience with atrial myxomas has only to increase.

The 24 patients with myxomas described here comprise a fairly large and a relatively unique group in that they represent a consecutive series from a single institution gathered over a 50-year period. Since the diagnosis of myxoma is a requisite for surgical excision, the combined surgical and autopsy experience represented by our patients should encompass virtually all in whom the diagnosis had been made either during life or at postmortem study from this institution.

Clinical presentation of myxomas

The clinical presentations of myxomas have been well recognized and are represented by the 24 patients reviewed. Myxomas are more common in women. Of our 24 patients, over 70 per cent were women, compatible with previous reports which have suggested a 75 per cent female sex incidence. Myxomas virtually always occur in adults. The average age of our patients was 50 years and none were under 24 years of age. The left atrium is the most common site of occurrence of the myxomas, present here in 92 per cent of our patients. Signs or symptoms of cardiac dysfunction are common either at the time the patient presents, or in retrospect, and almost always can be attributed to the presence of the atrial mass. The most common clinical cardiac problem is congestive heart failure which was present in over half of our patients. In only four patients, however was heart failure intermittent or was paroxysmal aggravation of heart failure present. In two patients there was a dramatic history of paroxysmal pulmonary edema unassociated with symptoms in between episodes. Although systolic precordial murmurs were described in half of the patients, a murmur of mitral stenosis was described in only nine patients. Thus although left

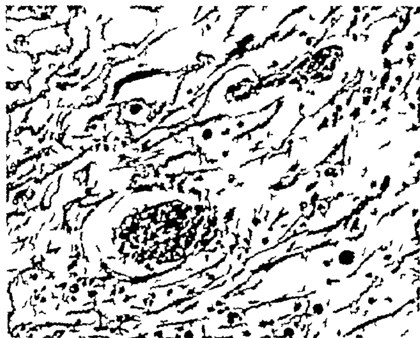


Fig. 3. Typical area of myxoma with loose strands of collagen, amorphous ground substance, macrophage undifferential mesenchymal cells, and vascular channels with very cellular walls. (Hematoxylin and eosin, original magnification ×250.)

atrial myxomas are the classical simulators of mitral stenosis, among our patients, less than 40 per cent of them had such a presentation. Embolism is another clinical clue to the presence of myxoma. In our patients it was relatively infrequent clinically occurring in five (21 per cent) patients. Although in four of the five patients with embolism, the emboli were to the brain and not readily approachable in the fifth patient, the diagnosis of left atrial myxoma was first suggested by histologic examination of an embolus surgically removed from the femoral artery. Not surprisingly the antemortem diagnosis and symptoms of myxoma regardless of type generally correlate with the size of the tumor.

The majority of the patients studied were in normal sinus rhythm and had normal or nonspecifically abnormal electrocardiograms. In three patients, atrial fibrillation had been present and in two of the three it was paroxysmal. The presence of normal sinus rhythm in a patient who is symptomatic with presumed rheumatic mitral disease might suggest the need to consider a mitral stenosis simulator. It is of interest that in one of our patients paroxysmal atrial fibrillation was the only clinical abnormality present which led to further evaluation and detection of her left atrial myxoma by echocardiography.

Diagnosis of atrial myxomas: past and prese[nt]

The natural history of atrial myxomas rem[ains] obscure, and accordingly the diagnosis of [the] atrial myxoma has always been a challenge. [As] recently as 1951 Pritchard commented t[hat] many believed "the diagnosis of cardiac tumor [is] either impossible or a matter of chance. In [our] group of 24 tumors the diagnosis was made du[ring] life in only half of them (Table III). It app[ears] from our patients, however that the chance [and] perhaps even the challenge of this diagnos[is are] rapidly diminishing with the technologic [ad]vances of the past 25 years. Before 1960, [nine of] the 11 (82 per cent) myxomas were undiagno[sed] during life and the two that were recognized [were] surprise findings at operation for presumed [rheumatic] disease. Prior to 1953 the diagnosis was m[ade] entirely at autopsy. The improved diagno[stic] methods have already affected mortality [rates] with only one of the 10 myxoma-caused dea[ths] occurring since 1960 (Table I).

Since 1960 only three of the 13 myxomas w[ere] unrecognized during life. Of those in whom di[ag]nosis was made and surgical therapy was in[sti]tuted six were recognized at cardiac catheteri[za]tion one by histologic examination by an em[bolic] femoral embolus, and three by echocardiograph[y] the latter being the most recent cases. Of [...]

three recent cases one had absent or minimal symptoms which would not have been sufficient to warrant cardiac catheterization, and it is likely that the diagnosis would not have been made as expeditiously without the noninvasive study. Thus, recognition of this lesion to a large extent reflects the diagnostic advances of the recent years. It is likely that with the ease of one-dimensional echocardiography and the increasing availability of two-dimensional echocardiography atrial myxomas as a clinical entity will increase, and hopefully along with this will come an improved understanding of their pathogenesis and natural history.

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Fundamentals of clinical cardiology

Re-entrant arrhythmias and concealed conduction

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I RE ENTRANT ARRHYTHMIAS

A re-entrant (reciprocal, Echo) beat is produced when the impulse generated in one chamber of the heart is propagated slowly through a path of depressed excitability and conductivity and returns to reexcite its point of origin after the end of the latter's refractory period. All forms of "re-entrant arrhythmias conform with the fundamental experiment of Mines in 1913, who stimulated excised coherent portions of the atria and ventricles in the electrical ray and frog. He noted that an atrial impulse conducted to the ventricles was reflected back into the atrium and vice versa, so that atria and ventricles contracted alternately—in reciprocation. Thereafter in the early electrocardiographic era, a number of isolated clinical observations were reported on the occurrence of reciprocal beating in man.

The prerequisites of the tissues responsible for re-entry have been studied experimentally and reciprocal beating of the ventricles has been reproduced in the dog heart.[14] Barker and associates suggested in 1943 that the clinical and electrocardiographic features of supraventricular tachycardia could best be explained by re-entry within the sinoatrial or A V nodes, a mechanism today firmly established by experimental studies in the animal and in man

Utilizing a modified diagram of the re-entry mechanism devised in 1928 by Schmitt and Erlanger[13] it was postulated that the presence in the A V junction of an unequally depressed region (Fig. 1) leads to delayed retrograde conduction (heterodromia) of a nodal impulse over the fibers with less marked depression and to unidirectional block (monodromia) in the fibers with marked depression.[24] Having passed the region of depression over less involved fibers, the retrograde A V junctional impulse now penetrates from above into the fibers which were blocked for retrograde conduction and returns to the point of its origin. Provided the time of retrograde conduction is long enough, the re-entrant impulse will find the pacemaker outside its refractory state and can discharge the pacemaker for a second time. The reflected impulse may then be conducted to the ventricles or may be blocked below the A V junctional pacemaker (concealed re-entry). At the same time, another attempt at retrograde conduction may occur and, depending on the same factors such as recovery of fibers responsible for retrograde conduction, this second retrograde impulse may or may not again reach the site where penetration into the pathway for forward conduction is possible (repeated re-entry).

The work of several investigators has validated this hypothesis of functional dissociation of pathways of conduction between the atria and ventricles.[25-27] Moe and co-workers[27, 28] introduced the concept of a dual A V conduction system based on indirect studies in the dog heart. They postulated that two functionally differing paths (α and β) are present in the upper part of the A V node converging into a final common path (FCP) in the subnodal area. Watanabe and Dreifus[29] demonstrated in the rabbit heart that propagation of impulses may fail in one portion of the A V node while another continues to conduct partially or completely Such dual or multiple pathways such

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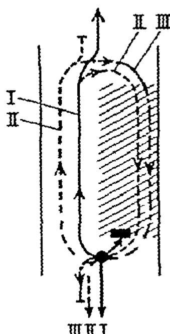


Fig. 1. Diagram of the mechanisms of single, repeated, and blocked (concealed) re-entry within region of unequal depression of the A V junction. (From Pick and Langendorf, Am. Heart J 40:13, 1950.) *The shaded area represents* part of the A-V junction (A V node or common bundle) of more marked depression that permits forward conduction but is blocked for retrograde conduction as indicated *by the short horizontal bar* (unidirectional block). An impulse *(I solid line)* arising in the A V junctional pacemaker *(solid circle)* is conducted down to the ventricles and—in retrograde direction—to the atria. The retrograde impulse, having slowly bypassed the region of retrograde block, now enters in forward direction *(II, dashed line)* the fibers blocked for retrograde conduction and returns to the pacemaker which had time to recover from its refractory period and may be discharged. The reentrant impulse *(II)* may give rise to reciprocal beat of the ventricles or may find the region below the junctional pacemaker still refractory (blocked or concealed re-entry). While re-entry to the ventricles is attempted or completed, the re-entrant impulse *(II)* may again penetrate into the fibers permitting retrograde conduction and may start second circuit leading, if completed *(III dot-dash line)*, to second discharge *of the junctional pacemaker* and to second reciprocal beat, or may be blocked below the pacemaker. In the case of the former occurrence, circulating movement within the A V junction and paroxysm of re-entrant (reciprocating) atrioventricular tachycardia may be initiated. (see text)

different functional properties, forming a loop in the A V or intraventricular Purkinje system with unidirectional block in one of its arms and slow conduction in the other has been accepted as the basis of many disorders of cardiac rhythm that can be summarily called Re-entrant Arrhythmias.

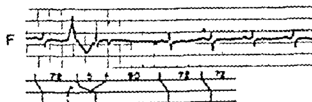


Fig. 2. Atrial echo (t) induced by P R prolongation consequent to an interpolated ventricular premature beat (see text).

Re-entry in the A-V junction

A single completed re-entry sweep within the A V junction gives rise to a premature contraction of the ventricles or the atria. Depending on the impulse origin proximal or distal from the potential re-entry loop—for instance, a depressed area in the A V junction—the re-entry will take place in an antegrade or retrograde direction and result in a "return extrasystole" or an "echo beat"[23-25] of the ventricles or the atria.

A common cause favoring occurrence of A V junctional re-entry is a premature contraction of the ventricles or atria, occurring spontaneously or reproducibly by artificial stimulation,[26] the necessary prerequisite being slow A V or V-A conduction.[27] A *ventricular* echo occurs when a premature ventricular (or A V junctional) impulse encounters in its retrograde propagation towards the atria relative refractoriness in the A V node associated with functional inhomogenity of its conducting elements. Retrograde conduction can proceed slowly only via one set of fibers, the α path, while the other β path is blocked by its longer refractory period but permits antegrade return of the impulse (provided that sufficient delay has occurred in the α path). However when the primary ventricular premature impulse is interpolated, the delay of the ensuing antegrade A V conduction of the next sinus impulse with its return in retrograde direction causes an *atrial echo* (Fig. 2). Thus with temporal physiologic refractoriness or abnormal depression of conduction, in conjunction with a unidirectional block in some fibers of the conduction system, the stage is set for a single or continued re-entry process and this applies not only for the A V junction but generally

In clinical ECGs problems may arise in distinguishing reciprocal beating in A V junctional rhythm from ventricular captures in some cases of incomplete A V dissociation.[*] The tw
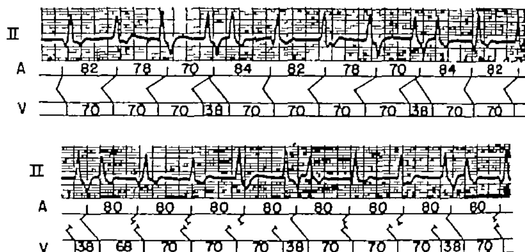


Fig 3 Double A-V junctional tachycardia. *The upper record shows reciprocal beating. The lower one shows* incomplete A V dissociation (see text). (From Pick and Langendorf, AM. HEART J 76:553, 1968.)

exist in the same tracing, as illustrated by Fig. 3. It demonstrates two portions of a long record obtained from a patient with double A V junctional tachycardia. On the basis of the regular atrial activity the early beats in the lower panel represent ventricular captures by the upper junctional pacemaker conversely the upper panel demonstrates reciprocal beating identified by prematurity of retrograde P waves sandwiched into the short ventricular cycles.

When re-entry in the A V junction is bidirectional, wherein an atrial echo follows a ventricular echo or vice versa, the arrhythmia may become self perpetuating and may be the cause of paroxysms of supraventricular tachycardia,[11-13] as illustrated in Fig. 4. In the record of April 4, 1966, a ventricular premature beat appears to be interpolated in the long sinus cycle. However the P wave buried in its ST T is distinctly premature, the subsequent sinus cycle is prolonged and shifted, and the distance between the two supraventricular beats that border the premature ventricular complex is shorter than the sinus cycle. All this indicates that the premature ventricular impulse, during prolonged retrograde conduction to the atria, has re-entered the A V junction to produce a single ventricular (reciprocal) beat. A similar event is seen at the start of the tracing of April 8, 1966. Here, however the mechanism continues as a circus movement within the A V junction, with 28 consecutive and alternating offsprings to the atria and ventricles, until it stops spontaneously Two P waves within the paroxysm, indicated by arrows, differ from the other frankly inverted ones. Both are atrial fu[sion] beats; in the upper strip a retrograde, in the lo[wer] strip an antegrade (sinus) impulse predomina[tes and] activates the atria. Thus, this tracing dem[on]strates how a *supraventricular* type of par[oxys]mal tachycardia may be initiated by an ecto[pic] beat of *ventricular* origin. [17]

Wallace and Daggett[17] demonstrated t[hat] atrial echoes can occur in the presence [of] complete A V block, thereby proving that [the] ventricle is not essential to the occurrence of [an] atrial echo Yet the question whether the atri[a, or] part of the atria, are invariably included i[n the] supraventricular re-entry loop has not been d[efi]nitely resolved.[44, 45] It has been shown that i[t is] possible to render the entire atrium refract[ory,] including tissue immediately adjacent to the A[-V] node, without abolishing the echo phenomen[on.] Also, ventricular echoes persist when atrial ac[tiv]ity is abolished by high potassium levels. T[hat] the atrium is not a necessary link in the re[-entry] pathway[21, 24, 43-4] is shown in Figs. 5 and 6. [In] Fig. 5 a sinus P wave is "sandwiched betw[een] the first couple compared to definite retrograd[e P] waves in the second and third couple. Retrogr[ade] P waves at a prolonged R P interval of 0.24 [sec] leave no doubt that the premature beats [are] ventricular echoes. However at the arrow a si[nus] P wave occurs within an identically spa[ced] couple. This proves that an emerging si[nus] impulse entering the A V junction prevented t[he] slow retrograde junctional impulse from enter[ing] the atria but did not prevent its reversal wi[thin] the junction, presumably the upper part of [the]

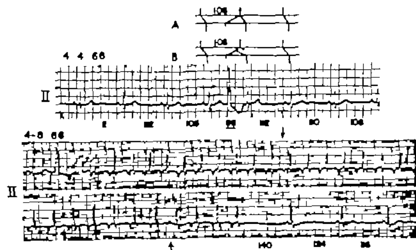


Fig. 4. Interpolated ventricular premature beat initiating paroxysm of reciprocating supraventricular (A V junctional) tachycardia (see text). (From Pick and Langendorf, AM. HEART J 76:553, 1968.)

A V node, to produce an echo in the ventricles.[57] In Fig. 6 similar groups of two or three fast beats follow A V junctional escapes in Leads III and V. In Lead III the retrograde P waves identify the arrhythmia as reciprocal beating. In Lead V_1, on the following day when atrial fibrillation had developed and the atria became unresponsive, the assumed reciprocal path would have to be below the atrio-nodal junction.[44]

Josephson and Kastor[58] recently observed that the atrium could be made refractory to retrograde atrial echoes during the tachycardia without interfering with the arrhythmia. They introduced premature atrial stimuli prior to the time the atrium would normally be retrogradely depolarized by atrial echoes. A pair of premature atrial depolarizations produced A V dissociation without terminating the tachycardia in one patient. The tachycardia could be initiated without an atrial echo in another patient. They concluded from their data that most, if not all of the atrium, is unnecessary for the initiation and maintenance of A V nodal re-entrant supraventricular tachycardia.

Re-entry *within* the A V node as the underlying mechanism of supraventricular tachycardia was established by recording from multiple microelectrodes in A V junctional tissue of the isolated rabbit heart preparation.[59, 60] Experimental studies in man by Bigger and Goldreyer[61, 62] proved that paroxysmal supraventricular tachycardia results from continuous re-entry through the A V node. Stimulated premature atrial depo-

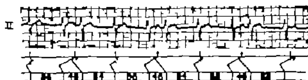


Fig. 6 Subatrial re-entry in A-V junctional rhythm with reciprocal beating (see text). (From Pick, AM. HEART J 86:249, 1973.)

larizations introduced during the relative A V refractory period initiated episodes of supraventricular tachycardia. In each patient test stimuli revealed a discrete zone within which re-entrant arrhythmia was reproduced. This echo zone was contained within the relative A V refractory period but distinct from the atrial vulnerable period, and has been defined by Goldreyer and Bigger as the range of coupling intervals in which premature atrial depolarizations uniformly result in either atrial echoes or supraventricular tachycardia. Stimulated premature atrial depolarizations introduced during sustained episodes of supraventricular tachycardia either altered its behavior or terminated it. They proposed that stimulated premature atrial depolarizations during supraventricular tachycardia entered the re-entrant pathway earlier in its relative refractory period and caused progressive conduction delay until conduction failed altogether with termination of circus movement.[62]

The use of artificial electrical stimulation of the heart has broadened our understanding about the mechanisms of tachycardia. A critically timed

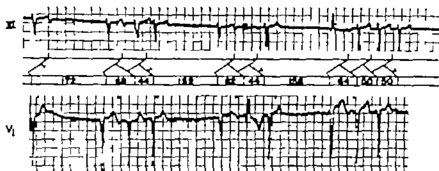


Fig. 6 Subatrial re-entry in A V junctional rhythm during atrial fibrillation (A V dissociation) in Lead V (see text)

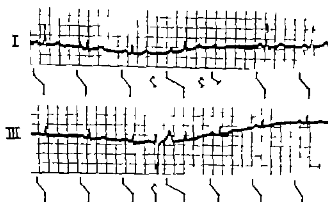


Fig. 7 First-degree and second-degree type I A V block imitated by blocked A V junctional premature beats. (Pseudo A-V block) (see text). (From Pick, Am. Heart J 86:249, 1973.)

premature beat can initiate tachycardia in the human heart in the sinus node, in the A V node[33-] in the ventricle,[35-40] and in cases of pre-excitation syndrome.[40] In the intact heart, initiation and termination of tachycardia by a premature beat given within a reproducible time interval strongly suggests a re-entry mechanism.[41] A critical degree of atrioventricular (A V) nodal conduction delay is required for the demonstration of manifest A V nodal re-entry and the initiation of A V nodal re-entrant supraventricular tachycardia Also sustained A V nodal re-entry requires a critical balance between conduction and refractoriness within the reciprocating limbs of the re-entrant circuit. Akhtar and associates[41] produced sustained atrioventricular (A V) nodal re-entrant tachycardia in five patients who had no prior historical or electrocardiographic evidence of supraventricular tachycardia with intravenous atropine Atropine enhanced A V nodal conduction and provided the required balance of conduction and refractoriness within the A V nodal re-entrant pathways to sustain A V nodal re-entry

Other investigators were able to demonstrate evidence of dual A V conduction discontinuous A V nodal curves (A A_2, H H) in a number of patients with A V nodal re-entrant paroxysmal supraventricular tachycardia (PSVT) using the extrastimulus technique and His bundle recordings.[44-46] They suggested that these curves reflected the presence of longitudinal dissociation of the A V node into fast and slow pathways. They also postulated that block in the fast pathway accompanied by antegrade slow pathway conduction allowed the fast pathway to recover and conduct retrogradely Wu and colleagues were able to support the hypothesis that discontinuous conduction curves reflect the presence of dual A V pathway as opposed to relative refractoriness within a single pathway utilizing critically timed ventricular extrastimuli.

Some features of atrial flutter may be due to re-entry circuit in the atrial tissue.[46-48] A circus movement can be established around the openings of venae cavae in the right atrium of dog heart by producing a premature beat early enough to cause unidirectional block.[48-49] Unidirectional block and re-entry would be more likely to occur from premature atrial depolarization if the atrial tissue is nonuniform with respect to refractory period, a condition found in disease processes or vagal stimulation.[48] Once the circus movement is established, atrial flutter will be sustained until the excitable gap of the re-entrant circuit is abolished.[70] It has been shown that atrial flutter could be terminated by atrial pacing at rates much slower than the rate of flutter One of the paced beats pre-excited the excitable gap and made it refractory to the returning impulse, as

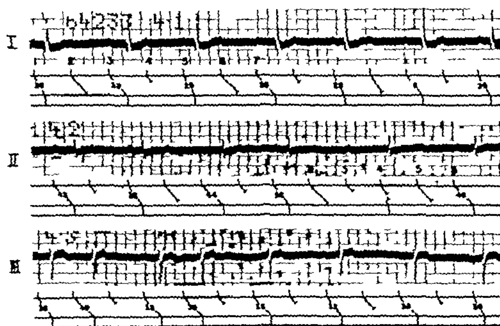


Fig. 8. Second-degree A-V block with concealed conduction. A-V conduction ratios vary between 1:2, 2:1, and 3:1 (see text).

that circus movement could be interrupted.[44]

Many of the features of atrial fibrillation are consistent with re-entry of multiple activation fronts. The re-entrant mechanism accounts for the observation of premature stimulation in its initiation, and for the presence of a vulnerable period—the limited time during the cardiac cycle in which fibrillation can be induced. The average atrial refractory period is shortened by vagal stimulation and this effect is inhomogeneous and results in marked disparity of refractory periods at various atrial sites.[45] The differences in recovery time represent a condition wherein a re-entrant mechanism of fibrillation is likely.

Re-entry in the ventricle

The concept of re-entry can explain the genesis of some of closely coupled ventricular extrasystoles.[46] When the excitability and conductivity were severely depressed in an ischemic area, premature responses were slowly conducted through the ischemic zone and frequently emerged to re-excite the surrounding normal tissue. This indicates that slow conduction of the *impulse through the ischemic area allowed the* normal tissues to recover their excitability in time to receive the re-entrant impulse emerging from the ischemic zone. This resulted in isolated extrasystoles or sustained tachycardia in the ventricle.

The study by Han and associates[47] supports the concept that some ectopic beats occurring in the ventricle with myocardial infarction are due to re-entrant circuits established between normal and ischemic zones due to difference in excitability and conductivity.

El-Sherif and associates[48] have shown after ligation of the left anterior descending artery in dogs that the infarction zone revealed the presence of continuous electrical activity bridging the diastolic interval between the initiating and re-entrant beats as well as functionally dissociated areas and areas of localized ventricular fibrillation. Conduction in a potentially re-entrant pathway showed a Wenckebach like pattern, with beat-to-beat increment of conduction delay leading to re-excitation of neighboring normal myocardium.

Using programmed stimulation and ventricular endocardial mapping of the human heart, Josephson and co-workers[49] also demonstrated that initiation of ventricular tachycardia was dependent upon development of a critical degree of fractionation of electrical wavefront in local left ventricular electrograms. They showed the presence of continuous electrical activity ("local fibrillation") spanning diastole and that termination of ventricular tachycardia necessitated cessation of this continuous activity.

Cranefield and Hoffman[43-44] had discovered the phenomenon of summation and inhibition in which a pair of Purkinje strands merge to form a single strand. The impulse in each of such a pair of fibers may be blocked in a depressed area but the subthreshold depolarizations spreading forward from each blocked impulse may summate to create a new impulse in the fiber formed by the union of two branches. On the other hand early arrival of one impulse may inhibit the area where the fibers join and may prevent the transmission of an impulse that would have been conducted. The phenomenon of unidirectional block, slow conduction summation and inhibition induced by depressing the excitability of a peripheral twig of the conducting system was shown to cause re-entry with regularity. Single circus movement can cause extrasystoles. Sustained circus movement can cause idioventricular rhythm and ventricular tachycardia.

Re-entrant arrhythmias involving accessory A V pathways

The clinical significance of ventricular preexcitation (Wolff Parkinson-White (WPW) syndrome) and its associated supraventricular arrhythmias was first reported in 1930. The frequency of this syndrome is seen in 1 of every 1 000 electrocardiograms and recurrent episodes of tachycardia are noted in 30 to 70 per cent of patients who exhibit the ventricular preexcitation abnormality. There were reports of sudden death with this syndrome, and ventricular fibrillation had been postulated as a possible mechanism. An anatomical basis for the shortcut of A V conduction has been established by finding accessory fibers bypassing partly or completely the normal A V junction.

In 1967 epicardial excitation mapping was introduced, and soon thereafter the use of His bundle recordings and electrical stimulation of the heart have brought new tools to the study of preexcitation and have clarified the mechanisms of the tachycardia. The information derived from programmed pacing techniques and the ability to reproduce and terminate the arrhythmias in the laboratory have resulted in the development of various means in the prevention of paroxysm of tachycardia. The ability to localize precisely the accessory pathways and the recent advances in the epicardial mapping studies enables the modern cardiologist to offer in selected patients, a surgical approach in the treatment of refractory arrhythmias associated with the WPW syndrome. Surgical correction of WPW syndrome when free wall A V connections are present can be accomplished with a high rate of success and a low operative risk.

The arrhythmias in the WPW syndrome

The most common rhythm disturbance in the WPW syndrome is a paroxysmal supraventricular tachycardia and is due to a re-entry mechanism. This can be induced in the laboratory by appropriately timed premature atrial or ventricular beats. When two atrial beats are produced in quick succession the first beat is followed by a QRS with maximal WPW deformity and preceded by a short P R interval. The second one is followed after a longer P R interval by a narrow and normalized QRS complex denoting block of conduction at the A V accessory pathway and sole propagation of the impulse in the A V node. During slow conduction in the normal pathway the A V accessory bundle recovers and is now receptive to conduct retrogradely the impulse back to the atria with a short R-P interval to initiate a reciprocating tachycardia. Most of the time the normal A V pathway provides the antegrade route from atria to ventricles and the A V accessory bundle serves as the retrograde path back to the atria, because the latter has a longer refractory period as compared to the former. Under these circumstances the QRS-T remains normal except when deformed by a development of a functional bundle branch block (aberrant ventricular conduction). Rarely antegrade impulse conduction occurs via the A V accessory bundle and retrograde propagation through the normal A V pathway producing widened and bizarre ventricular complexes, a pattern of a truly ventricular tachycardia.

Another form of tachycardia in the setting of ventricular preexcitation is the occurrence of atrial echoes giving rise to a reciprocating mechanism within the A V junction that is completely exclusive and independent of the A V accessory bundle inserting in the ventricles and that bears no relationship to WPW. This is supported by the finding that the tachycardia occurs at rates at which the A V accessory bundle would be inoperative, and by compensatory pauses following premature atrial or ventricular beats

that are observed during tachycardia.[illegible] An anatomical basis of this variant are additional anomalous A V tracts that bypass only part of the A V node and insert at its lower part.[illegible] At a critical time, the impulse forms a re-entry circuit comprising the upper A V nodal area that is remote from the A V accessory bundle. During the supraventricular tachycardia, each impulse is conducted through a portion of the distal A V junction. This may account for the inefficacy of drugs to reduce the number of transmitted impulses in cases of WPW and supraventricular tachycardias that are resistant to medical therapy. In these instances, A V accessory bundles of Kent type are responsible for the preexcitation pattern during sinus rhythm. However independent re-entrant circuits in and around the A V node probably with bypass tracts other than the Kent bundle are responsible for the supraventricular tachycardia.[illegible]

Atrial flutter–fibrillation in the WPW syndrome

The A V node normally through its filtering mechanism[illegible] protects the ventricles against rapid atrial rhythms. In the presence of an A V accessory bundle not possessing the protective property of the A V node, atrial flutter or fibrillation impulses can be rapidly conducted to the ventricle with life-threatening consequences due to immediate impairment of the hemodynamics. The refractory periods of the A V accessory bundle are important determinants of the resulting ventricular rate.[illegible]

Other investigators[illegible] have observed that an extremely fast and irregular rate with widened QRS complexes is characteristic when atrial fibrillation develops in patients with ventricular preexcitation during sinus rhythm. Estimation of the antegrade effective refractory period (ERP) of the A V accessory bundle can serve as an index of ventricular response that can be expected during atrial fibrillation, and by the same token retrograde ERP measurement of the same accessory bundle can provide an estimation of the maximal rate of re-entrant tachycardia that could develop.[illegible] For this purpose, the atria and ventricles should be paced from different sites to reveal antegrade and retrograde conduction over the A V accessory bundle and to accurately study its conduction characteristics.[illegible] Also, reports of multiple accessory pathways in patients with the WPW syndrome would seem to justify the utilization of comprehensive pacing from the right and left atria, right ventricle and, in selected patients, from the left ventricle and study of refractory periods to detect the presence of left sided concealed A V accessory bypass tracts[illegible] *(see below)*. It has been proposed that because of the relative frequent development of retrograde concealed conduction in the A V accessory bundle, the induction of atrial fibrillation during electrophysiological studies can provide a better insight as to the vulnerability to a very fast ventricular response over the A V accessory bundle and can allow a better selection of proper drugs in the prevention and control of atrial fibrillation in the WPW syndrome with its life-threatening consequences.[illegible] Recently Campbell and associates[illegible] found a 32 per cent incidence of atrial fibrillation associated with WPW in their study population of 100 patients. A statistically significant number eight of the 32 patients showing atrial fibrillation, had documented episodes of ventricular fibrillation. The elective initiation of atrial fibrillation has not been accompanied with morbidity although four cases required synchronized cardioversion to convert the arrhythmia back to sinus rhythm.

Concealed A-V accessory bypass tracts (concealed WPW syndrome)

In the last few years, there were numerous reports[illegible] of patients with recurrent episodes of supraventricular tachycardia and no electrocardiographic evidence of ventricular preexcitation during sinus rhythm. Electrophysiologic studies revealed the presence of A V accessory pathways capable exclusively of retrograde conduction (concealed WPW syndrome). This was attributed to their findings that the antegrade effective refractory periods (ERP) of the A V accessory bundle were usually long in the patients studied, and at a faster rate without ventricular preexcitation, conduction over the normal A V pathway was followed by concealed retrograde penetration of the A V accessory bundle, tending to enhance continued normal A V conduction.[illegible] The ventricular rate during atrial fibrillation appears to be determined by the antegrade refractory period of the A V node rather than of the A V accessory bundle. Concealment of the retrograde bypass penetration is not constant and may not be evident with slower atrial rate, as in atrial flutter.[illegible] The

following criteria for recognition of a concealed WPW syndrome were proposed

1 A recurrent or 'incessant form of tachycardia.

2 Spontaneous development of reciprocating tachycardias after sinus rate acceleration without antecedent premature atrial systoles or P R prolongation.

3 Retrograde P waves following the QRS complex in Leads II III AVF with P R intervals longer than the R P interval during reciprocating tachycardia.

4 Negative P wave in Lead I during the tachycardia a diagnostic feature of a concealed left sided bypass.

5 Slowing of the tachycardia rate and increase in the retrograde conduction time during ipsilateral bundle branch block.

6 The presence of atrial flutter/fibrillation associated with A V reciprocating tachycardia.

Other characteristics of concealed WPW syndrome include shorter cycle lengths of tachycardia, younger age group, and absence or low incidence of organic heart disease.

Of clinical interest is the report of a 60 per cent incidence of atrioventricular bypass tracts in patients with mitral valve prolapse, the majority of whom had a normal electrocardiogram. The high incidence of supraventricular tachycardia in the mitral valve prolapse syndrome appears to be related to left-sided latent bypass tracts.

The electrophysiologic basis of re-entry

Although re-entrant arrhythmias may occur in normal hearts, they are usually due to disease processes which change the electrophysiological behavior of cardiac fibers. Purkinje fibers are fast fibers and normally produce fast response action potentials which conduct rapidly at a velocity of 1 to 4 M /sec Disease may convert fast fibers to slow fibers by reducing the membrane potentials of the fast fibers, leading to inactivation of the inward Na current and of the fast response An action potential which is due to the slow current remains These action potentials conduct at very low velocities of less than 0.1 M /sec and are likely to develop unidirectional block. Localized areas with short recovery properties, existing together with slow conduction, enhance the genesis of re entrant activity These two electrophysiologic phenom-

ena are both present early in acute myocardial infarction, and may be important in explaining the high incidence of ventricular arrhythmias during its critical periods.

II CONCEALED CONDUCTION

The concept and the term "concealed conduction" were first introduced by Langendorf in clinical electrocardiography in 1948 and enlarged upon in later studies. The concept was based on the animal experiments of Engelmann in 1894 Erlanger in 1905, Ashman, Lewis and Master and Drury in 1925, and Lewis and Drury in 1926. It implies that an impulse may enter a conduction pathway without completely traversing it Since such a penetrating impulse does not reach its point of destination, partial (concealed) conduction can be determined in the surface electrocardiogram only in an indirect way that is, by its after-effects upon the formation or conduction of a subsequent impulse. The period of concealed conduction is very short and takes place during that portion of the conducting tissue cycle which represents the transition of absolute unresponsiveness to partial recovery and can sometimes be delineated within a range of a few hundredths of a second.

Langendorf and Mehlman first postulated that concealed A V junctional premature systoles could imitate first and second degree A V block and nonconducted premature atrial systoles. Based on deductive analysis of surface electrocardiograms, they proposed that blocked or nonconducted A V nodal premature systoles (concealed junctional premature systoles) may cause failure of atrial response ventricular response or both. Such concealed junctional depolarization may exert an effect on the conduction within the A V junction upon the subsequent sinus impulse and may represent the only evidence of a blocked A V nodal premature systole.

One example of such "pseudo-A V block" is shown in Fig. 7 It shows in Lead I sudden prolongation followed by failure of conduction in a regular sinus rhythm. As indicated in the diagram, this is attributed to the after-effects of two premature A V junctional discharges blocked in both directions. This interpretation is supported by Lead III, where the interpolated junctional discharge is conducted to the ventricles with aberration. Documentation of such a spon-

taneously occurring mechanism was provided by Rosen and associates[104] in a clinical case, using His bundle recordings, and was shown experimentally by Moore and associates[87] in the rabbit heart, recorded through a microelectrode impaled in the A V junction.

The concept of concealed conduction provides the key to the understanding of various otherwise unexplainable characteristics of simple and complex arrhythmias.[14] The most common manifestation of concealed *A V conduction* is the compensatory pause of ventricular premature beats and P R prolongation following their interpolation. It has been utilized by electrocardiographers in the interpretation of other conduction disturbances caused by premature systoles[147] [76-] of apparent irregularities of the A V junctional pacemaker in A V dissociation with or without A V block [71] [74] to explain irregularities of atrial and ventricular beating in complex arrhythmias, such as A V junctional tachycardia with unequal degrees of forward and retrograde block or in other unusual cases, for instance, ventricular parasystole complicating A V dissociation [73] or concealed interpolation in an A V junctional parasystole.[161] *The concept became valuable for* the understanding of the ventricular response in certain cases of atrial flutter[179] and the characteristic irregularity of the ventricular response in atrial fibrillation,[139] [77-170] for interpretation of certain cases of reciprocal beating,[81] [84,] [189] and the explanation of the failure of A V junctional escape beats to occur at the expected time during atrial fibrillation.[161] Failure to appreciate the role of concealed A V conduction in cases of second-degree A V block has led to errors in interpretations and unwarranted deductions.

Concealed retrograde *intraventricular* conduction was postulated in cases of preexcitation with atrial fibrillation[183-185] to account for the peculiar grouping of beats with normal and anomalous A V conduction, with transitional complexes or fusion beats inbetween. In these cases, an impulse conducted over one of the two available conduction pathways tend to enter the other path in a retrograde fashion and render it refractory for the subsequent supraventricular impulse. The occurrence of concealed conduction of the impulse within a re-entry path was postulated in certain cases of intermittent bigeminy due to ventricular premature systoles.[84] Such an incomplete penetration of the re-entry path may become manifest in an unexpected prolongation of the coupling of a subsequent premature systole,[76] or the failure of the premature systole to occur when expected.[14]

Langendorf[186] suggested that nonconducted interpolated A V nodal premature systoles could result in alternation of P R interval. The long P R intervals are due to the bidirectional block of the premature beats, their partial (concealed) forward conduction is responsible for the delay in conduction of subsequent sinus impulse. In 1965, Langendorf and associates[14, 186] were able to demonstrate and reproduce at will concealed A V conduction in the human heart using artificial cardiac pacing. Other investigators studied the mechanism of ventricular dysrhythmia associated with atrial fibrillation in the isolated rabbit heart with microelectrode techniques.[87] The variation in ventricular cycle lengths were caused by concealed conduction within the A V node. His bundle electrograms have shown that the phenomenon of repetitive concealed conduction due to an increase in atrial rate occurs proximal to the bundle of His,[187-189] a fact that was noted by Langendorf and Pick[190] five years earlier from *analysis of surface electrocardiograms.*

Thus, actual occurrence of partway penetration of impulses into potential conduction pathways, as demonstrated with the aid of intracardiac leads in electrophysiologic laboratories,[87] [88] [93-96] has substantiated the concept of concealed conduction originally derived from deductive reasoning. Hence, without recourse to modern recording methods, the diagnosis of concealed conduction can be confidently made in routine electrocardiography. For instance, and to return to the original observation of Langendorf and Mehlman,[180] a pseudo- A V block can be recognized in a surface electrocardiogram on the basis of (a) sudden unexplained P R lengthening[190-] (b) presence of both Mobitz type I and type II block in the same tracing[14] [66-] (c) the appearance of type II A V block in the presence of normal QRS complexes[67] [68] and (d) the occurrence of premature junctional systoles in some part of the record.[190, 192, 193]

Concealed conduction in second-degree A-V block

Concealed conduction can take place in both types of A V block.[200] In type I block, it usually occurs within the A V node and depresses subse-



Fig. 9 Concealed (blocked) reciprocal beating in A V junctional rhythm with delayed retrograde conduction (see text) (From Pick and Langendorf, Am. Heart J. 40:13, 1950.)

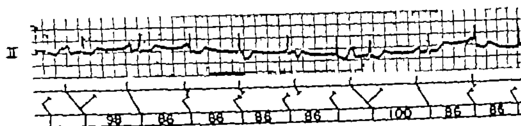


Fig. 10 Concealed retrograde re-entry in incomplete A V dissociation. (see text) (From Pick and Langendorf, Am. Heart J 6 553, 1968.)

quent impulse conduction. Re-entry concealed on the surface electrocardiogram may cause typical or retrograde Wenckebach periods demonstrable on the His bundle electrogram. Re-entry with collison of depolarization wave fronts within the A V node or proximal His-Purkinje system may account for the failure of the last ventricular impulse to be conducted to the atria during Wenckebach cycles. Block of two consecutive P waves during Wenckebach A V block is due to deep penetration of the A V junction by the first "blocked" sinus impulse, reducing or preventing penetration of the next sinus impulse. His bundle studies in such cases show repetitive block proximal to the His bundle. Depth of concealed conduction within the A V junction may not be the only determinant in the response to a subsequent impulse. The speed at which successive impulses partially invade the A V junction may decline progressively and may set the limit to the number of impulses consecutively involved in the repetition of concealment (Wenckebach of concealed conduction).

Prolonged periods of ventricular standstill may develop when concealed conduction affects both rhythmicity and conductivity of A V junctional tissues in a repetitive manner (repetitive concealed conduction). In Mobitz type II concealed conduction takes place in the pathway down to the region of block, where it discha[rges] subsidiary A V junctional or fascicular pace[mak]ers and prevents their escape.

Concealed re-entry in the A-V junction (concealed reciprocation or abortive echo)

This denotes a re-entry mechanism in w[hich] the reflected re-entrant impulse fails to reach to depolarize the chamber of its origin, yet af[fects] formation or conduction of a subseq[uent] impulse. Some investigators believe that r[eciprocal] responses are so easily induced in an[imal] hearts that their observations are co[nsider]ed normal physiologic property. The im[pulse] *initiating* re-entry may itself be either manif[est or] concealed. Manifest re-entry may become [con]cealed by altering the cycle length of ventr[icular] stimulation, and concealed re-entry ca[n be] detected by cessation of ventricular pacing a[t an] opportune time in the cardiac cycle.

Selected unusual examples of concealed A V conduction

Fig. 8 shows a second-degree A V block of I with varying A V conduction ratios. In Le[ad] in the beginning of Lead II and at the e[nd of] Lead III there is 2:1 A V conduction with a[lter]nation of the ventricular cycle due to altern[ation] of the (prolonged) P R interval of the cond[ucted]

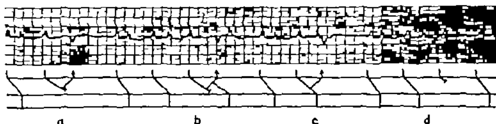


Fig. 11 Second-degree type I A V block with concealed A V conduction with three atrial echoes and single ventricular echo (see text). (From Pick, Am. Heart J. 80:249, 1973.)

beats. The assumption in the diagram is that the greater lengthening of every other P R interval is caused by penetration into the A V junction of the preceding "blocked" sinus impulse. This is substantiated by occasional completed conduction of such impulses (in the beginning of Lead III), changing the conduction ratio to a 3:2 ventricular response, as well as by one instance of block of a P wave following concealed conduction (Lead III) temporarily changing the A V ratio to 3:1 which permits an A V junctional escape.

In Fig. 9 is reproduced an unusual case of slow A V junctional rhythm, wherein R P intervals and junctional cycles alternate concomitantly due to concealed antegrade re-entry postponing the next junctional discharge. The diagram shows that the prolongation of the ventricular interval to 1.24 or 1.28 sec. is the aftermath of junctional re-entry completed in the middle with aberrant ventricular conduction but concealed at the beginning and the end of the tracing. The spontaneous junctional beat becomes reset to a similar extent, by 0.24 sec.

Longitudinal functional dissociation in the A V junction of antegrade pathways to the ventricles and retrograde pathways to the atria may readily resolve some arrhythmias which appear complex, as shown in Fig. 10. In this instance of complete A V dissociation caused by nonparoxysmal A V junctional tachycardia, the regular sequence of the ectopic beats is disturbed by pairs of ventricular captures, the first of which has a prolonged P R interval. Yet the distance between the captured beats is not shorter as expected, but 0.12 to 0.14 sec. longer than the junctional cycle of 0.88 sec. In order to account for this failure of a junctional beat to occur on time, a reversal of the slowly conducted impulse can be postulated to occur *somewhere within the A V junction*, distal from the site of the ectopic pacemaker (concealed

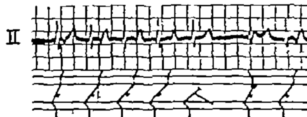


Fig. 12. Concealed retrograde conduction and concealed antegrade A-V junctional re-entry in accelerated A V junctional rhythm with type I second-degree retrograde A-V block (see text). (From Langendorf and Pick, Europ. J. Cardiol. 1:11, 1973. Reproduced by permission.)

re-entry). This attempted atrial echo, while not reaching the atrial level, discharges on its way the A V junctional pacemaker and thereby postpones its next spontaneous firing—permitting one more capture of the ventricles by a sinus impulse, as shown in the diagram.

Unusual effects of concealed A V conduction in a second degree A V block are shown in Fig. 11. Four different events are marked *(a)* to *(d)* for presentation. Part *(d)* shows a simple 3:2 Wenckebach period. In *(a)* to *(c)*, the sequence of regular sinus impulse is disturbed by atrial echoes initiated by greater delay in antegrade conduction. These echoes occur regardless of whether the initiating sinus impulse reaches the ventricles, as in *(c)* or fails to do so, as in *(a)* and *(b)*. However when it fails, the unused portion of the antegrade path offers a potential avenue for a ventricular echo, a sweep that is actually completed in portion *(b)*.

In Fig. 12, the first part of the record shows an accelerated A V junctional rhythm with suppression of impulse formation in the sinus node due to retrograde depolarization of the atria. The retrograde conduction time progressively lengthens until, after the fifth QRS, the retrograde P fails to appear. A ventricular pause occurs exceed

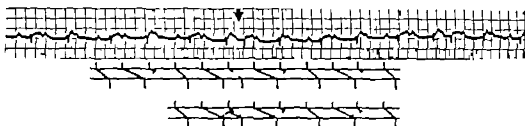


Fig. 13. Functional longitudinal dissociation and concealed A-V junctional re-entry in second-degree type I A-V block. Pseudo supernormal phase of A V conduction (see text) (From Pick, Am. Heart J 86:249, 1973.)

ing the regular junctional cycle by 0.34 sec. The returning junctional beat coincides with the P wave of an escaping sinus impulse after which regular junctional rhythm with retrograde P waves is resumed. The regular junctional sequence has been reset by an attempt at a ventricular echo that failed to reach the ventricles. This antegrade re-entry attempt was initiated by maximal delay of the retrograde impulse that proceeded to the point of re-entry but did not reach the atria—as shown by the absence of retrograde P after the fifth QRS. Thus, the above rhythm disturbance involved two mechanisms—(a) concealed retrograde conduction causing (b) a concealed ("abortive") ventricular echo. Furthermore, this tracing illustrates that in man the atrium is not a necessary link in the re-entry circuit

Fig. 13. reveals that in the middle of a Wenckebach period *at the arrow* the P R interval, after having increased from 0.28 to 0.46 sec., unexpectedly shortens to 0.24 sec. before its increment is resumed and the period is completed. In the past such a paradoxical P R shortening was attributed to a supernormal phase of conduction in a depressed A V junction. However with recent insights gained in experimental and in clinical studies with intracardiac electrodes, the following interpretations seem to be more likely and are illustrated in the two ladder diagrams. In both, functional dissociation of two A V conduction pathways is postulated In the upper diagram, antegrade conduction at a critical point occurs via a path with a long refractory period but a faster conduction speed indicated by the dashed diagonal line The lower diagram shows the premature QRS to be unrelated to the P wave preceding it It is attributed to a ventricular echo reflected from a concealed (abortive) attempt at an atrial echo when P R has reached a critical delay Subsequently n th r ventricular echo, after similar P R pr l ngati n is prevented by penetration of the "blocked" sinus impul[illegible] into the re-entry circuit. Again, the entire re-entry phenomenon would occur at a substa[illegible] level of the A V junction.

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Clinical pharmacology of the new beta-adrenergic blocking drugs
Part 1 Pharmacodynamic and pharmacokinetic properties

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The findings that the relative potency of a series of sympathomimetic amines varied with the effector organs or systems led Ahlquist in 1948[1] to conclude that there were two distinct types of adrenergic receptors. Ahlquist classified them as α and β receptors. The distribution of these receptors is shown in Table I, which also shows some of the responses produced by activation of these receptors. β-adrenoreceptors have subsequently been further divided into two main groups, β_1 receptors in the heart and β_2 receptors in the bronchi and blood vessels.[2-4]

Until the discovery of dichloroisoprenaline (DCI) by Powell and Slater in 1958, Ahlquist's theories were the subject of a great deal of scepticism. The discovery that DCI selectively blocked responses which according to Ahlquist were mediated by β-receptors has proved to be one of the most exciting developments in human pharmacology

The beta blocking agents which were developed after DCI, due to the pioneering work of Black, were initially conceived as a means of treating angina pectoris. However it soon became clear that beta-blocking agents had much to offer in other clinical settings. The application of these agents has been accelerated by the development of drugs possessing a degree of selectivity for various subgroups of the beta receptor population. More controversial has been the introduction of agents with varying degrees of intrinsic sympathomimetic activity (agonist effect).

Table I Distribution of adrenoceptors

Organ	*Receptor*	*Effect of stimulation*
Heart	β	Increase in heart rate
	β_1	Increase in cardiac contractility
	β_1	Accelerated A V conduction
Bronchi	β_2	*Dilatation*
Blood vessels	β_2	Dilatation
		Constriction
Eye		Dilatation of pupil
Gastrointestinal tract	and β	Reduction in motility

A useful range of beta-blocking drugs is now available to the clinician in most Western countries; however only propranolol is approved by the FDA for clinical use in the United States. Other beta blockers have yet to be marketed in this country because of FDA requirements of long-term human as well as long-term animal studies before final approval is made. These extraordinary requirements are based on questions of safety that have been raised by the tumorgenicity of some of these agents (practolol, alprenolol) and a severe cutaneous occular peritoneal syndrome seen with practolol.[5-8]

The carcinogenicity study requirements have been met for many of these newer beta blockers (acebutolol, metoprolol, nadolol, pindolol, oxprenolol, and timolol) and long term studies of these agents are now in progress in this country

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Table II Pharmacological properties. Some differences between β-adrenoreceptor blocking drugs

Drug	*Synonyms*	*Beta-blockade potency ratio (propranolol-1)*	*Cardio-selectivity*	*Partial agonist activity*	*Membrane stabilizing activity*
Acebutolol	Sectral M & B 17,803A	0.3	+	+	+
Alprenolol	H56/28 Aptin Betaptin Betacard	0.3	0	++	+
Atenolol	ICI66082 Tenormin	1	+	0	0
Metoprolol	H93/26 Lopresor Betaloc	1	+	0	±
Oxprenolol	Ciba 39089 Ba Trasicor	0.5-1	0	++	+
Pindolol	LB46 Visken	6	0	+++	+
Practolol	ICI50172 Eraldin	0.3	+	++	0
Propranolol	ICI45520 Inderal Avlocardin	1	0	0	++
Sotalol	MJ1999 Betacardone Sotacor	0.3	0	0	0
Timolol	MK 950 Blocadren	6	0	±	0
Isomer d-propranolol		0.1	0	0	++

Most of the beta blockers presently under study in this country or marketed abroad appear to have virtually the same useful and adverse effects as propranolol. However differences in metabolism, passage through the blood–brain barrier direct effects on membranes, and degrees of intrinsic sympathomimetic activity may ultimately prove clinically meaningful.

In this article the pharmacodynamic and pharmacokinetic properties of the newer beta-blockers will be discussed along with propranolol and practolol for comparison. In the following articles the clinical applications of these agents related to their differing pharmacologic properties will be addressed and in the final two articles clinical data concerning one of these newer beta blocking agents currently under investigation by our group will be presented.

Differences in pharmacodynamic properties (Table II)

All the beta blocking drugs are specific antagonists.[19] Thus stimulation of beta adrenoreceptors in the heart, irrespective of the manner in which that stimulation is evoked can be blocked by beta-adrenergic blockers. However, the response to agents which stimulate contraction of the heart by other pathways such as calcium or digitalis is unaffected.

Beta-blocking potency Beta blocking drugs are competitive inhibitors of the effects of catecholamines at β-adrenoreceptor sites. They reduce the effect on a sensitive tissue of any concentration of agonist in such a way that the dose response curve is shifted to the right, a given tissue response requiring a higher concentration of agonist in the presence of the drug. β-blocking potency is judged by the inhibition of the tachycardia produced by isoproterenol. As shown in Table II, pindolol and timolol are mg. for-mg the most potent, and acebutolol, alprenolol, practolol, and sotalol the least potent β-blocking agents.

Structure–Activity–Relationship. The chemical structures of beta adrenergic blocking agents (Fig. 1) have several features in common with isoproterenol. The 2-C side chain with an alkyl substituted secondary or tertiary amine seems to determine the affinity for the beta receptor. The larger the alkyl group the greater the affinity for

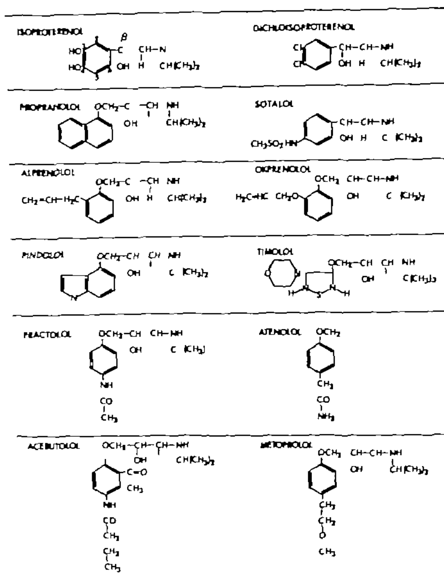


Fig. 1 Structural formulas of available beta-blocking drugs.

the beta receptor[13] The particular structure attaches to the receptor site and the nature of the substituents on the aromatic ring determines whether the effects will be predominantly activation or blockade. The configuration of the asymmetric beta carbon of the side chain is crucial for pharmacologic activity Beta blocking drugs exist as pairs of optical isomers. However almost all of the beta blocking activity resides in the levorotatory isomer For propranolol and alprenolol,[14] the (−) levoratatory isomers were up to 100 times more active that the (+) dextrorotatory isomers. Only the racemic mixture of each drug consisting of equal parts of the two isomers is available for clinical use. The different stereoisomers of beta-adrenergic blocking drugs are useful for differentiation between the effects of beta receptor and nonspecific properties (i.e., local anesthetic properties possessed by both forms) but clinically the (+) dextrorotatory isomers are of no value (Table II).[13]

Membrane stabilizing activity This property sometimes referred to as "quinidine-like or "local anesthetic action, is unrelated to competitive inhibition of the actions of catecholamines and is exhibited equally by the two optical isomers of the drug.[13] These properties were originally defined electrophysiologically propranolol,[14] oxprenolol,[15] alprenolol, and acebutolol all reduce the rate of rise of the intracardiac potential without affecting the over-all duration of the spike or the resting potential. The concentration

of propranolol at which this effect has been demonstrated in vitro with human ventricular muscle is approximately 50 to 100 times the propranolol blood level associated with the inhibition of exercise-induced tachycardia. With other β-blockers the difference is even greater and it is unlikely that plasma levels associated with "quinidine-like" effects are clinically significant. The anti-arrhythmic effects of these drugs have been shown to be due to beta blockade, unrelated to the membrane stabilizing effect. Practolol, which is without membrane effects, in equipotent doses is as effective an anti-arrhythmic agent as propranolol (with membrane properties).

Intrinsic sympathomimetic activity (ISA) Beta-blockers, by definition antagonize the action of agonists on the beta adrenoreceptor. Of the β-blocking drugs listed in Table II propranolol, sotalol, timolol, atenolol, and metoprolol cause no observable effect when they interact with β receptors in the absence of a primary agonist such as epinephrine or isoproterenol. Paradoxically the others—acebutolol, alprenolol, oxprenolol, pindolol, and practolol—cause a very small agonist response, indicating that they themselves stimulate as well as block the receptor. The partial agonist activity of β-blocking drugs differs from that of epinephrine or isoproterenol in that the maximum response which can be obtained is less, although the affinity for the receptor site is high.

On theoretical grounds it may be postulated that beta blockers displaying ISA are less likely to induce cardiac insufficiency than beta blockers devoid of such activity since the former will diminish the force of contraction of the heart muscle to a lesser extent. However therapeutic studies have yet to demonstrate this supposition. It is of interest that beta blockers exhibiting no ISA such as propranolol cause an increase in pulmonary capillary wedge pressure and in cardiopulmonary blood volume, whereas those drugs with ISA such as oxprenolol and pindolol either exert no influence on pulmonary capillary wedge pressure or actually lower it while at the same time producing less of an increase in cardiopulmonary blood volume. Beta blockers which possess an intrinsic sympathomimetic effect lower the heart rate less markedly and thus entail less risk of provoking excessive bradycardia. However a significant part of this excessive bradycardia results from unopposed or enhanced vagal activity once the sympathetic tone has been inhibited.

There is no good evidence that beta-blocking drugs with ISA (oxprenolol) are inherently unsafe in patients at risk from beta-blockade (asthmatics) than those without. However pindolol, a drug with the most ISA among the beta-blockers now in use, has been shown to be bronchoprotective in many patients intolerant to propranolol because of bronchospasm.

Cardioselectivity (Table II) β-blockers may be classified as selective or non-selective according to their relative abilities to antagonize β-receptors in some tissues at lower doses than are required for others. Cardioselective beta blockers inhibit the cardiac beta receptors (β_1-receptors) but exert little influence on the bronchial and vascular beta receptors (β_2-receptors) when employed in low dose.[27] Of the metabolic effects mediated by beta receptors, insulin release and liver and muscle glycogenolysis are mediated markedly by β_2 receptors, but there is still doubt about the nature of the beta-receptor mediating renin release and lipolysis. The fact that the cardioselective beta blockers have little or no effect on the peripheral beta receptors should theoretically have two advantages.

1. First, these agents would be safe to employ in cases where the patients were suffering or had suffered from bronchial asthma. Cardioselectivity is of undoubted therapeutic value, as has been shown in clinical trials in asthmatic subjects in which practolol caused a lower incidence of respiratory side effects than did propranolol. However other investigators have commented that some cardioselective beta blockers (practolol and acebutolol) may increase bronchial obstruction due to differences in asthmatic patients.

2. Secondly beta blockers with cardioselectivity might also appear suitable for the treatment of hypertension because their use would involve no inhibition of the peripheral (vasodilator) beta receptors. In practice, however cardioselectivity is diminished at the usual doses required for treatment of hypertension.[27]

Acebutolol in small doses, atenolol, metoprolol and practolol (the so-called cardioselective blockers) are 50 to 100 times more active in inhibiting the effect of isoproterenol on heart rate and force of contraction (β_1 receptors) than on smooth muscle of the bronchial tree or peripheral blood vessels (β_2 receptors). The separation is evidently not absolute, and at higher doses β_2 ...

Table III Pharmacokinetic parameters of β-blockers

Drug	Extent of absorption (% of dose)	Extent of bioavailability (% of dose)	Dose-dependent bioavailability	Variation in plasma level	Beta-blocking plasma concentrations	Per cent bound		Lipid solubility†
						Serum proteins	HSA*	
Acebutolol	—	—	—	—	0.2 2 μg/ml	—	—	—
Alprenolol	>90	≈10	Yes	10-20 fold	50-100 ng/ml	85	38	strong
Atenolol	—	≥40	No	low	0.2-0.5 μg/ml	—	—	—
Metoprolol	>95	≈50	N	7 fold	50-100 ng/ml	12	12	weak
Oxprenolol	70-95	24 60	No	5 fold	80-100 ng/ml	—	—	weak
Pindolol	>90	≈100	No	4 fold	50-150 ng/ml	—	57	weak
Practolol	>95	≈100	N	—	1.5-5 μg/ml	—	12	weak
Propranolol	>90	≈30	Yes	20 fold	50-100 ng/ml	93	62	strong
Sotalol	—	≥60	—	4 fold	0.5-4 μg/ml	—	54	—
Timolol	>90	—	—	—	75-10 ng/ml	—	—	—

*HSA = Human serum albumin.
†Lipid solubility determined by the distribution ratio between octanol and water

Table IV Elimination characteristics of some orally administered β-adrenoreceptor blocking drugs[11]

Drug	Elimination half-life (h)	Total body clearance (L/min)	Urinary recovery of unchanged drug (% of dose)	Total urinary recovery (% of dose)	Active metabolites of clinical importance
Acebutolol	about 8	—	—	—	—
Alprenolol	2-3	1.2	<1	>90	Yes
Atenolol	6-9	—	≈40	—	—
Metoprolol	3-4	1.1	≈3	>95	N
Oxprenolol	2	0.6	—	70-95	—
Pindolol	3-4	0.4	≈40	>90	N
Practolol	6-8	0.14	>90	>90	No
Propranolol	3.5-6	1.0	<1	>90	Yes
Sotalol	5-12	—	≈60	—	—
Timolol	4-5	—	≈20	65	—

nism becomes apparent. Cardioselectivity is therefore dose-dependent and decreases or disappears altogether when larger doses are used.[20] This is in sharp contrast to drugs having ISA where with higher doses the ISA effect remains undiminished.[21]

At this juncture the exact basis for cardioselectivity is not understood.

Differences in pharmacokinetic properties (Tables III and IV)

The pharmacokinetics of propranolol has been studied more intensively than almost any drug in the history of pharmacology. Soon after its introduction, its plasma concentration was demonstrated to be much lower and more variable after an oral rather than an intravenous dose, although the drug was quickly and completely absorbed from the gastrointestinal tract.[22, 23] This variance in bioavailability was found with other beta blockers and in this section the pharmokinetic differences between drugs will be discussed.

Absorption. All the beta-blocking compounds are well absorbed over a wide part of the small intestine except for atenolol. Absorption is fairly rapid, peak concentrations in the blood occurring 1 to 3 hours after administration. The absorption of "sustained release" preparations of alprenolol or oxprenolol is more prolonged and lower peak blood levels are achieved.[11, 22]

Bioavailability of orally administered drugs. With some drugs which are extensively metabolized by the liver *some of the administered dose* fails to reach the circulation after oral administration despite complete alimentary absorption because the drug in the portal vein is taken up and removed by the liver before it can appear in the systemic circulation. Both propranolol and

alprenolol undergo extensive obligatory presystemic hepatic ("first pass") elimination. In addition, following the oral administration of single doses, the relationship between bioavailability and dose is not proportional, the availability of small doses being quite low.[1] As the dose is increased, progressively more drug reaches the systemic circulation. These data suggest than an avid hepatic extraction pattern becomes saturated with larger doses. This "first pass" effect may explain the wide variability in plasma concentrations seen in patients receiving the same dose of drug. This kinetic situation applies to the disposition of not only propranolol and alprenolol, but also to oxprenolol.[13]

One important consequence of the high first pass metabolism of propranolol is that an intravenous dose of the drug represents a much larger amount in proportion to the oral dose than would appear from the number of milligrams administered.

The bioavailability of other β-blocking agents is given in Table III. Pindolol has somewhat different kinetics than propranolol and alprenolol after both oral and intravenous administrations, and it is unlikely that first pass metabolism is important.[14] Practolol is the least extensively metabolized of the beta adrenoreceptors, 90 per cent being eliminated from the body unchanged (no "first pass" effect).[13]

Lipid solubility and protein binding (Table III)

Beta blockers vary widely in their lipid solubility and plasma protein binding characteristics.[13] Propranolol and alprenolol have the highest degree of lipid solubility. This greatly influences the distribution volume of these drugs and may bear on their ability to cross the blood–brain barrier. Animal studies have shown that the highly lipid soluble drugs equilibrate rapidly between the brain and the plasma. Practolol[36] and metoprolol[37] have a low degree of lipophilicity.

Binding to various protein fractions in the blood has a significant effect in the pharmacokinetic and pharmacodynamic properties of drugs. Generally only the unbound fraction of the drug is considered effective and in relating the pharmacological effect to the plasma concentration. Only the free fraction of drug should therefore be used.[38] It is also generally appreciated that the degree of protein binding can have a pronounced effect on the elimination kinetics of drugs, particularly on those with high affinity for the proteins.

Binding of β-blockers to various serum proteins has only been studied to a minor extent and the methods used in different investigations have varied. It is difficult to make relevant comparisons between reported results. It is, however, quite obvious that the degree of binding varies considerably between different compounds, in spite structural relationships.

Johansson and colleagues[39] found that alprenolol is bound to about 85 per cent of serum proteins at therapeutic serum levels, whereas the binding of the less lipophilic drug metoprolol was only about 12 per cent.[39]

Volume of distribution, drug clearance, and halflife (Table IV)

The beta-blockers so far studied are rapidly distributed in the body. The apparent volume of distribution varied three- to four fold between the compounds, but in all cases the apparent volume of distribution exceeds the physiological body [illegible] space.

The beta blockers are rapidly eliminated from the body and most of them have an elimination half life between 2 and 4 hours. The shortest half lives are found with those drugs which are extensively metabolized (practolol having the lowest rate of elimination). Even with respect to elimination, the various beta blockers show a diversified pattern which appears to be associated with the lipid solubility of the drug.[34] Highly lipid soluble drugs like alprenolol and propranolol are, for instance, almost completely eliminated by various metabolic systems in the liver. As the lipid solubility decreases, the renal excretion however becomes more important and this mechanism appears to be almost entirely responsible for the elimination of practolol (low lipid solubility).[36] Between these extreme examples of the elimination pattern of beta-blockers, there are several drugs for which both biotransformation and renal excretion significantly influence elimination as shown by the ratio of unchanged drug and metabolites in the urine (Table IV). The urinary recovery of unchanged drug in this table refers to oral administration. For those compounds with a pronounced hepatic "first pass" elimination effect (alprenolol, propranolol), the fraction of the dose excreted unchanged in the urine will be substantially higher after intravenous administration.[37]

The mode of elimination of the different beta blocker compounds may have clinical relevance in patients with renal and hepatic disease. As practolol is mainly eliminated by the kidney it can be expected that decreased renal function should have a pronounced effect on the pharmacokinetics of the drug. For practolol, a linear increase relationship between the plasma half life and creatinine clearance has been obtained by a number of workers. Bodem and co-workers found an up to sixfold increase of the plasma half life, and in uremic patients with a glomerular filtration rate below 3 mL/minute plasma half lives over 100 hours have been recorded for practolol. During dialysis a considerable shortening of the half life was found.

Sotalol is also mainly excreted via the kidneys as an unchanged drug, and in patients with end-stage renal failure, the plasma half life for sotalol was on the average 42 hours compared with 5 hours in normals.

Despite its being 40 per cent eliminated by the kidneys, the half life of pindolol was not affected by renal disease, there being previously a concomitant increase in metabolic clearance as renal clearance was reduced.

The effects of liver disease have not been investigated but for those drugs having a high hepatic clearance, a reduction in clearance and a prolonged half life would be expected for several reasons including reduced hepatic flow decreased enzyme activity and decreased protein binding.

The deviations of the elimination rate of β-blockers would appear to imply that therapy with these agents should be started at lower doses in patients with liver disease (if the drug is mainly eliminated via metabolism in the liver) or renal disease (if the drug is mainly eliminated as unmetabolized drug). It might be advisable to monitor plasma levels of the drugs in patients with liver or kidney diseases.

Relationship between dose, plasma level, and efficacy. Beta blockers that are largely metabolized by the liver show large inter individual variation in circulating drug concentrations after a given oral dose, probably because of the first pass effect (alprenolol, propranolol) and because of genetic differences in the rate of drug metabolism (Table III). The variation is less for drugs largely cleared by renal mechanisms (practolol) provided that renal function is not impaired.

A wide variation exists also between plasma concentration of beta blockers, which is associated with any given therapeutic effect. There have been many explanations posed to explain this phenomena. First, patients may have different levels of "sympathetic tone" and a greater concentration of a given beta-blocker would be required to achieve the desired therapeutic result. This was shown by our group with propranolol, where large differences in plasma drug levels were associated with the same pharmacological effect. Secondly many beta-blockers have flat plasma response curves which means that the plasma concentration may vary considerably within a very narrow effect interval.

Another reason might be the formation of active metabolites (not measured in plasma assay) in varying amounts in different individuals. This might, for instance, be the case with propranolol and alprenolol, which both form active metabolites of clinical significance.

Despite the lack of correlation between plasma levels and inter-patient therapeutic effect, there is some evidence that a relationship does exist between the logarithm of the plasma level and the beta blocking effect (blockade of exercise-induced tachycardia or isoproterenol-induced tachycardia). The beta blocking plasma concentrations for the different compounds are shown in Table III.

Several authors have reported that the duration of the beta-blocking effect is considerably longer than indicated by the elimination half lives of the beta blockers. A pronounced decrease in the plasma concentration with time may therefore not be associated with a parallel decrement in clinical effect. This has been demonstrated in clinical practice since it has been shown that many of the beta blocker compounds can be administered twice daily.

Conclusion

Although beta-blocking compounds have similar therapeutic effects, they have different pharmacological properties. Understanding these differences may enable the clinician to select a specific compound in a given clinical situation.

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Annotations

The place of coronary surgery in the treatment of arteriosclerotic heart disease (ASHD)

This report discusses the state of surgery for coronary disease, a subject in which I have been interested and active for the last 40 years. The number of cases operated upon annually now approach 100,000. Survival curves published by medical centers with extensive catheterization and operative experience show an initial decrease in mortality rate for the first year and a continuing spread throughout the ensuing five years.

Catheterization is now accomplished easily with a mortality of less than 0.25 per cent. The Sones and Judkins techniques appear to have equal safety records. Many teams decide upon which to use according to the individual problems of the patient. If there is concomitant atherosclerosis in the femoral vessels or in the aorto-iliac vessels, the brachial approach will be used. Approximately three catheterizations are done for each actual operation performed.

Many distinguished physicians still do not believe in surgery for coronary disease. They present statistics which controvert ours and show that under current medical management, coronary patients perhaps live as long without surgery as they do after an operation, and they point out that prostaglandin inhibitors, particularly thromboxane inhibitors such as aspirin, Indocin, and now Anturane, which are undergoing extensive clinical trials, are expected to shortly overtake the advantages of the surgical approach. Nevertheless, I believe it is generally agreed that surgery has a definite role to play in the over-all picture.

For a large proportion of patients treatment with nitrates and propanolol, reduction of the risk factors, and graduated exercise programs constitute the basic and accepted treatment for stable angina pectoris. A patient is not referred for surgical treatment until his primary care physician has referred him to another cardiologist, one who is associated with a cardiopulmonary laboratory where he is given exercise tests and finally coronary angiography. Patients are selected for cardiac surgery after a committee of cardiac surgeons and cardiologists has reviewed all the data of the case, including the electrocardiograms, exercise tests, echocardiograms, catheterization data, ventriculography and coronary angiography and possibly the new isotope studies.

The spectacular difference between operated and unoperated patients is not longevity but the quality of their lives. Those who have had successful surgery can go about their business, return to their work, and escape the constant dread of the fearful pain in the chest that denies almost every pleasure of life and bodes the time when an attack will be fatal. Often patients with angina abandon sexual activity because they fear that it will bring on this terrible pain, and their mates often unconsciously avoid sexual contact out of genuine concern for their husband or wife. In exploring this aspect of the benefits of the procedure, in recent conversations with Mason Sones and Don Effler [illegible] concurred that one of the most gracious benefits of the procedure is the re-establishment of the normal sexual relationships, particularly in patients between the ages of 50 and 60.

There are many ways of accomplishing direct revascularization. At first it appeared that the saphenous vein of the thigh was the most satisfactory although some advocated direct anastomosis of the internal mammary arteries. It soon became apparent that more than two or three anastomoses were necessary, that the upper saphenous vein was too large for the smaller distal vessels, and the internal mammary arteries too small and not long enough to provide flow to multiple placements, and so the saphenous vein of the leg achieved the present place of honor as being the autograft most commonly employed. What is the particular advantage of the sural saphenous vein? The answer comes quickly to us when we think of the pressure relationships in the coronary circulation.

Physiologically there are two distinct sets of coronary arteries, the epicardial and the intramyocardial; the former being on the surface of the heart are not subjected to the rising pressures of myocardial contraction during systole. Actually the greatest flow into the epicardial coronaries is during systole, although flow also continues throughout diastole. On the other hand, in the short almost vertically directed branches which constitute the intramural arteries, flow is rapidly diminished even to the point of reversal during systole due to the mounting pressure of the contracting myocardium. Thus during diastole the myocardium receives its influx, but during systole the epicardial vessel must distend or balloon to accommodate the increased volume of blood to be delivered to the myocardium in the following diastolic phase. Because the vein grafts are reversed, the valves they contain help prevent reflux into the aorta during diastole, and because they are quite distensible, they provide a good volume of blood to be delivered to the myocardium during diastole. This ballooning of the vein grafts during systole and emptying during diastole may be easily observed when the patient comes off bypass.

The saphenous vein in the thigh ordinarily contains about three valves and three or four communicating or confluent branches. The saphenous vein in the leg, which is quite large and sustains a higher venous pressure because of its distance from the heart, ordinarily has six or more valves and may have twelve tributaries or communicators. For this reason it has been concluded that the sural saphenous vein is more desirable despite the extra effort in removing it from its bed.

Skip grafts, sequential grafts, snake grafts, and circular grafts have all been recently introduced and have taken their place when there are many areas of the myocardium into which it is necessary to provide a new blood supply particularly in those patients that have multiple obstructions throughout the coronary arborizations. In planning multiple anastomoses, mapping the courses of the grafts and the sites

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to be anastomosed by utilizing measurements and markings on an umbilical tape *before* the decompression of the heart is a worthwhile precaution and recalls the old adage: Measure your cloth ten times, my son. You can cut it but once.

Various types of probes and dilators are being used to ascertain and assure patency of the anastomoses and outflow essels. Endarterectomy of distal segments after dilation is again becoming common practice, and instruments reminiscent of those I originally designed for this purpose in the 1950' are making their reappearance. It is becoming evident that the assurance of distal runoff is important for long survival. It is fortunate that only the epicardial coronaries are involved in the atherosclerotic process. The intramyocardial vessels ha e long been demonstrated to be virtually free, allowing the surgical approach to be confined to the surface of the heart. Using optical magnification, fine sutures, and embodying Jaboulay and Carrel principles in avoiding constricture t the suture site, 85 or 90% patency of the individual anastomoses is being achieved. It has been found advantageous to lea e a few short lengths of branches on the graft which facilitates introduction of the aforementioned probes and other instruments after the anastomoses are completed. These provide channels for intraluminal pressure and flow measurements as well as for intraoperative coronary angiography

The oidance of air emboli, particularly the cerebral, is accomplished nowadays through canula inserted into the left entricle through the left atrial appendage. Some use a single right trial canula and omit venting the ventricle. Air is removed from the aorta by simply inserting small needles before the patient comes off bypass.

Cooling of the patient during bypass has long been useful adjunct in preserving the myocardium and preventing surgical shock. Dennis Melrose original method of cardioplegia with potassium has been revived using lower concentration of potassium with the addition of glucose and markedly lower temperature. The coronaries are infused by cross-clamping the aorta and inserting cannulas abov and below the clamp. The one abov delivers the oxygenated blood perfusing the body and the lower delivers the almost freezing Ringers, potassium, glucose solution into the coronary circulation, arresting the heart for the necessary period during which the anastomoses are made between the eins and the coronary arteries.

One particular apparatus and its judicious use has begun to enlarge the scope of coronary surgery. With the aid of the preoperative, intraoperative, and postoperative intraaortic balloon assistance immediate operations within 4 hours are being performed successfully and with acceptable mortality rates upon patients with early evidence of life-threatening pain, myocardial infarction, as well as preinfarction angina. New enzyme evaluations, including the presence in the urine and serum of m oglobin, gi an early clue to the transition from myocardial ischemia to necrosis and infarctions.

Computerized radioisotope studies are now being developed and have show the capacity t demonstrate clearly selected areas of impaired motion of the entricular w ll. Improvement in entricular function ma be show in postoperati patients with this non-invasi technique which in the preoperative state revealed reduced entricular output and immobile segments.

The aim of revascularization in the m [illegible] of ischemia and necrosis is to limit the amoun f mu le tissue lost. There is no w y to reclaim the tissue d on erted into excretory products by the [illegible]. The intraaortic balloon pump was originally introduced for particular reason—to salvage people in cardiogenic shock secondary to myocardial infarction. Its application to intraoperative and postoperative situations has increased the safety of coronary operations. It has been particularly useful in weaning patients from extracorporeal circulation and thus saving their lives. When it seems that the patient is doomed to die when the pump is turned off, and after repeated efforts have been made to wean the patient off the pump, the intraaortic balloon pump will save 50 to 75 per cent of the patients, particularly if initiated early. It is now practically essential to have an intraaortic balloon pump in any hospital that has a heart surgery program.

Finally the procedure's ability to lower mortality seems to be enhanced, as in many other fields of technology, with experience. Teams that ha e worked together for 3 or 4 years naturally do better than new teams. Then of course, there is the virtuosity of the gifted surgeon which proves that surgery is an art as much as it is science.

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Treating lipid disorders

Cholesterol and triglycerides are transported in blood in the form of lipoprotein complexes. Lipoproteins are usually separated out either by electrophoresis or ultracentrifugation. They are classified into three main groups in ultracentrifugation analysis high density lipoproteins (HDL), low density lipoproteins (LDL) and very low density lipoproteins (VLDL). The respective terms in electrophoretic analysis are alpha- beta- and pre-beta-lipoproteins.

Many observations have suggested that HDL may protect against coronary heart disease (CHD). The earliest of such reports were published quarter of a century ago by Barr and associates[1] and by Nikkila. Unfortunately these pioneering observations were largely forgotten and research into the association between blood lipids and CHD has come to be focused mainly on total cholesterol and LDL. It was not until 1975, when Miller and Miller[2] reported lower HDL in CHD patients than in matched controls, that great scientific interest in the topic was initiated, resulting in several epidemiological studies which have confirmed the findings.[3-6] The protective role of HDL against atherosclerosis is also suggested by the longevity of subjects with familial hyper-alpha-lipoproteinemia.

Besides clinical studies, the protection afforded by HDL against coronary therosclerosis is supported by in vitro experiments suggesting that HDL may participate in the transport of cholesterol out of therosclerotic lesions. LDL is commonly considered to have an opposite effect.

Perhaps the most interesting study concerning HDL has recently been published by Nicolosi and co-workers.[8] They found that feeding two monkey species (squirrel monkey and [illegible]us) with experimental coconut oil chow resulted in similar [illegible]grees of hypercholesterolemia. In the squirrel monkey the increase was mostly in the LDL fraction, while in the cebus the rise was in HDL. Squirrel monkeys developed fatty streaks and atheromatous plaques in the aorta, whereas the cebus monkeys remained free of lipid deposition. It is also worth noting that primates transporting their cholesterol primarily as HDL are resistant to atherosclerosis, while species which circulate much of their cholesterol as LDL, such as man, the pig, and most monkeys, are prone to the disorder.

As most research over recent years into the role of lipids in the pathogenesis of CHD has been focused on total cholesterol and LDL, it is not surprising to find that the classical lipid hypothesis as an explanation for CHD remains controversial.[9] If there are two components with opposite actions, it is their ratio which would presumably determine the net result.

The pharmaceutical industry has provided us with a number of so-called hypolipidemic agents for reducing elevated blood lipid levels, and the reductions in blood cholesterol and triglycerides so achieved are well documented. However it remains unclear whether any improvements in life-expectancy have resulted from such treatmen[illegible] Reductions in myocardial infarctions have been similarly disappointing.

Growing awareness of the inverse relationship between HDL and CHD prompted us to investigate our own fi[illegible] in clofibrate-treated subjects with respect to HDL [illegible] months we gave clofibrate as a hypolipidemic agent at a [illegible] dose of 1,500 mg. to 52 hyperlipidemic subjects [illegible] plasma cholesterol above 7.7 mmol/L, or triglyceride [illegible] 2.0 mmol/L, or both. Twenty-five were of type IIA, 20 of ty[illegible] IIB, and seven were of type IV. After treatment the mean values for cholesterol, triglycerides, LDL, VLDL, and to[illegible] lipids were significantly decreased, whereas the mean HD[illegible] concentration remained virtually unchanged in type IIA a[illegible] IIB subjects. There was a slight increase in mean HDL in ty[illegible] IV subjects. The individual responses of HDL among all ty[illegible] II subjects varied considerably and occurred in a similar w[illegible] in type IIA and IIB subjects. With types IIA and IIB pat[illegible] combined a decrease in HDL was seen in 16 subjects and a[illegible] increase was seen in 21, while in the remaining [illegible] the HDL concentration remained unchanged. In contra[illegible] LDL was decreased in all but one.

According to the HDL concept the incidence of CHD [illegible] inversely related to the level of HDL. If this represents [illegible] causal relationship, we must begin to question the [illegible] treating hyperlipidemic subjects with hypolipidemic agents [illegible] we do now. Reductions obtained in plasma total cholester[illegible] triglycerides, LDL, and VLDL cannot necessarily be [illegible] to counteract the effect of decreased HDL, since the associa[illegible]tion of these risk factors with CHD is more equivocal and the associated risk is less marked.

We suggest that treatment of hyperlipidemia and the use [illegible] hypolipidemic agents should be re-evaluated. Firstly [illegible] to improve understanding, we should begin with the [illegible]ogy. If low HDL predisposes to CHD it is not a "hyper[illegible] disease, but just the opposite. Both normolipidemic [illegible] hyperlipidemic subjects can have low HDL values. Statisticall[illegible]y HDL is inversely related to plasma triglyceride (VLDL).[10] Type IIA subjects typically have higher HD[illegible] than type IIB subjects and in type IV subjects even low[illegible] HDL values are usually noted.

It should be remembered that the classical Fredrickson typing of hyperlipidemias does not take HDL into accoun[illegible] The classification is based, in essence, on cholesterol (LD[illegible] and triglyceride (VLDL) values in plasma. Interestingly, [illegible] clinical value has been questioned by Fredrickson himself, even before the recent reappraisal of HDL. The classificat[illegible] has served as a valuable tool in research and for understandin[illegible] the biochemical mechanisms involved in hyperlipidem[illegible] With the growing awareness of HDL, however, the clinic[illegible] value of the typing seems to be less important. It seems [illegible] we should begin speaking of lipid disorders and their manage[illegible]ment.

Secondly we must learn to use our present drugs to grea[illegible] advantage. The basis for their use is, of course, an accura[illegible] evaluation of the lipid picture of the patients. Conventional ultracentrifugation for HDL analyses is too laborious f[illegible] clinical work. Other simple methods have been sought[illegible] Agarose gel electrophoresis is simple and fairly reliab[illegible] though not ideally accurate. Manganese-heparin precipita[illegible]tion gives fairly true picture of HDL alues. In our experien[illegible] however the most practical method for HDL determinatio[illegible] seems to be PEG-6000 precipitation, hich is technica[illegible] simple and gives results comparable with ultracentrifuga[illegible]tion. When HDL is analyzed as HDL-cholesterol, the critic[illegible] stage seems to be the cholesterol assay. Generally HDL cholesterol is in the range 1 to 2 mmol/L. Many laborator[illegible] may not use methods sensitive enough to accurately d[illegible]

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mine these cholesterol levels, or changes of even smaller magnitude induced by treatment (T Gordon, personal communication). In our experience the most reliable method, and one which is not too laborious, is the FeCl technique.

Our present proposal for the drug treatment of lipid disorders therefore is that in addition to the conventional lipid analyses, measurement of HDL should be performed initially If HDL is high, the need for treatment is questionable. After 2 to 3 months of active treatment, the measurements of triglycerides, total cholesterol, and HDL should be repeated. If there is no response, or there are negative changes as indicated by decreased HDL, alternative treatment should be attempted.

Finally disappointing results from the current use of drugs for improving life-expectancy in patients with lipid disorders call also for new agents in their treatment. It has been suggested that the next generation of these drugs should not aim primarily at reducing elevated plasma lipid levels, but rather at increasing HDL. At present we know that physical activity and moderate alcohol intake usually tend to increase HDL. Recommendations of regular alcohol consumption *for that purpose are sure* to raise objections. Changing fat saturation in the diet does not change the total cholesterol/HDL–cholesterol ratio.

In conjunction with the study involving clofibrate we have had an opportunity of testing new compound, gemfibrozil, for the treatment of hyperlipidemia in 30 type IIA and IIB subjects. HDL-cholesterol was measured by the PEG-6000 precipitation method. The mean value rose from 1.15 mmol/L to 1.45 mmol/L, an increase of 29 per cent, and the ratio HDL-cholesterol/total cholesterol increased from 0.147 to 0.217 Both changes were highly significant. In none of the subjects was HDL decreased during the 6 months treatment, and only three patients failed to respond to the rather low dosage of the drug used. Similar results have been reported elsewhere, indicating that effective pharmacotherapeutic ways of elevating plasma HDL will soon be available.

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Pulmonary edema following radiological investigation of patients with peripheral occlusive vascular disease Adverse reaction to contrast media

The widespread hemodynamic changes following the injection of organic water-soluble contrast media have been attributed to the composition and hypertonicity of the media. Osmolarity of these solutions can be 5 to 10 times that of normal plasma Hypotension may follow the injection and is apparently due to a direct effect of the hyperosmolar solutions on the vascular smooth muscle The other main side effects reported are an increase in cardiac output, small increase in stroke volume, and a transient rise in left ventricular end-diastolic pressure A sudden rise in plasma volume occurs, with concomitant rise in plasma osmolality and fall in hematocrit A 10 per cent increase in plasma volume after 2 minutes and 5 per cent increase after 5 minutes have been noted, after 30 to 40 ml. of 75 per cent sodium iothalamate.

In the period June to December 1976, 68 patients with intermittent claudication in the Queen Elizabeth Hospital, Birmingham, underwent aortofemoral radiography under general anesthesia The patients were aged 24 to 79, the majority being between 60 and 70 years. Of these 68 patients, five developed pulmonary edema Shehadi[*] reported only six cases of pulmonary edema in 112,003 radiological investigations with contrast media The over-all incidence of non-fatal reactions being 2 3 per cent, and those developing pulmonary edema represented 0 06 per cent of the total

All 68 patients underwent percutaneous femoral arteriography with a Seldinger technique with visualization of the distal descending aorta and peripheral vascular tree During the procedure the arterial catheter was flushed with physiological saline containing heparin (1,000 units/L) via standard intravenous administration set with a Fenwal pressure infusor bag. The rate of infusion was not closely controlled, nor was the volume administered, except on four occasions when it varied from 300 ml to 1 25 L I no case did the volume exceed 1.5 L.

Three contrast media were used (Conray 280" (1 450

Table I Contrast media doses

	No pulmonary edema		Pulmonary edema	
	Patients	Mean dose in ml.	Patients	[illegible]
Conray 280 as radiological screening dose	58	17.5	5	[illegible]
Conray 280 as sole agent	3	106 6	0	[illegible]
No Conray 280	2	0	0	17.5
Conray 325	44	116	3	[illegible]
Conray 325 and Conray 420	2	45	[illegible]	[illegible]
Conray 420	14	98	2	[illegible]

mosmol./L.), "Conray 325 (1,700 mosmol./L.) and "Conray 420" (2,300 mosmol./L.). The least hypertonic, Conray 280 was used in all cases for radiological screening to check the position of the catheter within the aorta. In three cases Conray 280 was used as the sole contrast agent (total volumes 110 ml., 130 ml., and 80 ml.). In all other cases the more hypertonic Conray 325 and Conray 420 were used for the main radiographic procedure. The range of total doses injected was 60 to 175 ml. (Conray 325) and 60 to 300 ml. (Conray 420)

No single anesthetic technique was used for all the patients but all received barbiturate (1 per cent methohexitone or per cent thiopentone) followed by nitrous oxide oxygen and relaxant (alcuronium 15 to 25 mg., pancuronium 4 to 8 mg

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gallamine 80 to 120 mg.) with controlled entilation. If supplementation was necessary either fentanyl (0.05 mg. to 0.1 mg.) or halothane (0.5 to 1 per cent) was used. Anesthesia lasted an average of 75 minutes.

The amounts of contrast media administered in the study varied widely The mean volume of contrast media was slightly higher in patients who developed pulmonary edema than in other patients, but the numbers relative t the scatter were too small for statistical analysis. In order to obtain satisfactory radiological examination further doses abov the 20 to 30 ml. recommended (May and Baker) may hav to be given.

Of the fi patients who developed pulmonary edema, three had pre-existing central cardiovascular disease in addition to their claudication. One of the three had had myocardial infarction 2 years before admission, one had atrial fibrillation (rate controlled to 70 to 90 beats/minute) and the third had essential hypertension (B.P 200/100 mm. Hg) with left ventricular hypertrophy The other two patients were free from major heart disease. However one of these patients did receive 200 ml. of Conray 420.

Anesthesia was uneventful in four of these fi patients. The pulmonary edema became apparent clinically 2 to 3 minutes after relaxant reversal and was confirmed radiographically There was no evidence of residual curarization. Treatment consisted of 100 per cent oxygen and intravenous frusemide (40 to 80 mg.) initially but three of the four patients required artificial ventilation with positiv end-expiratory pressure for 12 to 18 hours. The fifth patient developed pulmonary edema during anesthesia, 3 minutes after the main contrast injection (110 ml. Conray 325). This responded to frusemide 80 mg. intra enously and reco ery from anesthesia was uneventful.

It would appear that the de elopment of pulmonary edema is multifactorial. Firstly the hemodynamic changes associated with the injection of contrast media already mentioned and the subsequent inappropriate use of large volumes of physiological saline as the arterial flush solution, combined with the olumes of hypertonic contrast media required for adequate aortofemoral aortography

As one apparently fit patient developed pulmonary edema after 200 ml. of Conray 420, this olume should not be exceeded. There should be substantial reduction in the volume of contrast media used in patients with history or evidence of myocardial infarction, myocardial ischemia, or hypertension. Any further depression of the myocardium—e.g., after neostigmine—may well precipitate the attack.

Therefore, patients undergoing retrograde femoral arteriography should be given careful preoperati cardiological assessment. Monitoring of the preoperati fluid infused, the olume, and the nature of the contrast media and the volume of arterial infusion fluid administered seems essential.

The hemodynamic changes associated with the administration of hyperosmolar radiographic contrast media combined with those changes associated with pre-existing arteriosclerosis may well result in pulmonary edema.

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Of when is a physician prepared?

When a young physician wise enough and trained enough to make medical decisions affecting the lives of hundreds of other people, especially people to whom he is not related and about whom callous attitude is likely to exist? This moment of great decision by young physician cannot occur when he is an undergraduate medical student, nor one second after he crosses the stage and receives his diploma at commencement exercises. He has the legal right to make medical decisions as soon as he has been certified to practice medicine by his state examining board. But, that certification occurs only few day after he receives his diploma. Nevertheless, he is not yet prepared to practice medicine. So, when is he prepared? Young trainees, such as house staff, begin making hazardous diagnostic and therapeutic recommendations which influence the lives and young families of patients few minutes or hours after beginning an internship. Is this proper? Is the young trainee ready to make wise decisions? If not, when is he ready? And, who is to decide when he is ready? How is the decision to be reached? Are the present method and practice correct? This all needs careful consideration. Why not start such considerations now!

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Letters to the Editor

Clearances of propranolol and quinidine

To the Editor

In the report by Kessler and associates on "Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol, which appeared in the November 1978, issue of the AMERICAN HEART JOURNAL (96:627, 1978) were included data in Table II which showed that the mean clearance (Cl) of quinidine in the control group was 5.0 ± 0.4 mL/min./Kg. compared to a clearance of 3.1 ± 0.6 mL/min./Kg. in the propranolol group. It was noted that this was a statistically significant difference. The authors indicated that the volume of distribution (Vd) was decreased, but not significantly. The authors commented that since quinidine is not highly extracted, hepatic flow dependency would not be expected to cause such a reduction in clearance.

The authors calculated clearance using the formula, $Cl = \frac{Dose}{AUC}$. Since all the data were not available in the article, the individual calculations could not be rechecked. However it is possible using the relationship $Cl = \frac{0.693\ Vd}{t_{1/2}}$ to verify the data in Table II. Using the relationship, we found that the control group data were internally consistent. However in the propranolol group the $t_{1/2}$, Vd, and Cl values for patients No. 6, C. G. and No. 7 S. R. were not internally consistent— Cl for C. G. was calculated to be 4.6 rather than 1.7 and Cl for S. R. was 2.2 rather than 0.9. The mean clearance for the propranolol group incorporating the newly calculated values is 3.8 ml./min./Kg.

Using these data the difference in clearance between the control group and the propranolol treated group is less than originally reported. Without the raw data, it can only be said that the data in Table II for patients No. 6 and No. 7 of the propranolol treated group are not consistent with the relationship

$$Cl = \frac{0.693\ Vd}{t_{1/2}}$$

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Steady-state plasma concentrations of quinidine and propranolol

To the Editor

We read with interest the recent publication by Kessler and associates[1] (AM. HEART J. 96: 627, 1978). The authors conclude that quinidine clearance and volume of distribution are reduced in patients receiving propranolol therapy compared to a group of control patients. In that study the pharmacokinetic parameters of quinidine alone and quinidine with propranolol were not determined in the same [illegible] Ideally quinidine disposition should be examined in the [illegible] subjects with and without propranolol coadministration. [illegible] addition, as the authors correctly point out, the [illegible] parameters of quinidine volume of distribution and clea[illegible] cannot be calculated from oral data unless one knows [illegible] fraction of the dose which is absorbed intact into the [illegible] circulation (*i.e.*, bioavailability). We have recently c[illegible] a study whose purpose was to examine the steady-[illegible] plasma concentrations of quinidine in the same subjects [illegible] to and after establishing steady-state propranolol [illegible] concentrations. Although our study will form the [illegible] more extensive communication, we thought it [illegible] briefly report our findings, as they contrast with [illegible] Kessler and colleagues. Five healthy subjects received [illegible] quinidine sulfate orally every 6 hours prior to and [illegible] tant with 60 mg. propranolol every 6 hours. Quinidine [illegible] concentrations were determined during a 6-hour [illegible] val. Areas under the 6-hour quinidine plasma conce[illegible] tion-time curves (AUC) were determined and the [illegible] steady-state plasma concentrations ($\bar{C}$) [illegible] ($\bar{C}$ = AUC/6 hour). The average quinidine steady-state [illegible] ma concentration (± standard deviation) prior to and [illegible] propranolol therapy were, 2.34 ± 0.74 µg/ml. and 2.0 ± [illegible] µg/ml., respectively. There was no statistically [illegible] difference between these values using a Student's paired [illegible] ($p > 0.05$) nor were there any differences in the [illegible] quinidine plasma concentrations achieved during a [illegible] interval at steady-state. Our data indicate, in contrast to [illegible] conclusions of Kessler and co-workers, that quinidine [illegible] ance does not change in the presence of propranolol [illegible] subjects and at the drug doses used in the present study [illegible] greater than expected quinidine plasma concentrations [illegible] indeed be seen in patients for a variety of reasons, [illegible] suggest that propranolol will not by itself alter the [illegible] of quinidine. As a result, there appears to be no need [illegible] upon this pharmacokinetic information, to reduce [illegible] doses in subjects receiving propranolol.

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Reply

To the Editor

Reed, Talbert, and Ludden are indeed correct that the [illegible] clearance of quinidine in our propranolol group should [illegible]

1.8 ml./min./Kg. vs. 5.0 ml./min./Kg. in our control group. Dr. Mayersohn and colleagues, using multiple oral quinidine dosage, and Dr. Ochs and colleagues, using intravenous quinidine dosage, have demonstrated findings consistent with normal quinidine clearance and volume of distribution in normal subjects receiving propranolol. Nevertheless, our finding of unusually high serum concentrations of quinidine after an initial 200 mg. oral loading dose in patients receiving propranolol represents raw data. This finding is still of concern since, as pointed out in our paper, it indicates potential dangers in the practice of giving higher initial loading doses of quinidine. Whether the difference in our results vs. Mayersohn and colleagues finding regarding peak quinidine concentrations after oral dosage is due to single vs. multiple dosage regimens, experimental technique, or the populations studied (normals vs. patients with cardiac disease) is unknown at present. Although both Mayersohn and Ochs information is reassuring for the many patients with arrhythmias and essentially normal cardiac function, some caution is still advised when initiating quinidine therapy in patients with cardiac dysfunction who are receiving propranolol.

We are grateful to Dr. Mayersohn, Mr. Reed and their colleagues for their interest, careful scrutiny and response to our article.

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Post PVC pressures in normals and in patients with abnormal LV function

To the Editor:

The article by Hamby and associates[1] (Am. Heart J. 96:195, 1978) is correct in pointing out that the systolic pressure in the proximal aorta in the first sinus beat following a PVC is normally less than in the preceding beats. Those patients with abnormal left ventricular function show post PVC overshoot, with or without transient pulsus alternans. This fact is very poorly appreciated and is liable to generate confusion in the minds of bedside clinicians who know from experience that except for patients with IHSS everyone overshoots following PVC. The reason behind this paradox becomes clear when one records the post PVC pressure in a normal patient with frequent spontaneous PVC' as one withdraws an arterial catheter from the left ventricle to the aortic bifurcation. The post PVC systolic pressure is less in the left ventricle and in the ascending aorta. At the aortic arch it is roughly the same, and it is higher in the descending thoracic and abdominal aorta.

The reason normal patients undershoot and abnormal patients overshoot is probably not terribly complex. The extra aortic runoff during a compensatory pause is usually around 30 c.c. If the stroke volume is increased by more than 30 c.c., the pressure will overshoot and if it is less than 30 c.c. it will be less than in the control beats. Angiographic analyses of the post PVC stroke volume in normal subjects reveals a small increase of 5 to 15 c.c. Since this is less than the extra arterial runoff, the systolic pressure "undershoots." The post PVC beat in those with abnormal left ventricular function increases disproportionately from 30 to 100 c.c. Because this is more than the extra runoff, the pressure overshoots.

Observing the left ventricular pressure response to an induced PVC prior to left ventricular angiography in hundreds of patients over the past five years has confirmed the view that this provides a quick, safe, and reliable index of left ventricular function. Occasionally this maneuver will uncover the characteristic super-overshoot providing the first clue to the diagnosis of IHSS.

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REFERENCE

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Reply

To the Editor:

I thank you for giving me the opportunity to comment on Dr. Eyer's letter regarding my article on "Postextrasystolic aortic pressure pulse response in coronary artery disease" (Am. Heart J. 96:195-202, 1978).

The postextrasystolic pressure response, as commented on by Dr. Eyer, may be affected not only by the state of the left ventricular myocardium, but by the site at which the pressure is being recorded. The pressure-pulse contour when recorded in a peripheral artery is well known to be altered in terms of both contour and peak pressure when compared to the central aortic pressure-pulse. We had hoped to use the carotid pressure pulse recording by non-invasive methods as a screening technique to evaluate left ventricular function, but did note that the postextrasystolic peak pressure response was different in the carotid when compared to the central aortic pressure response. Such a difference can be well explained by pressure-pulse contour changes taking place in a peripheral artery. The mechanism for the findings noted in the central aortic pressure after an extrasystole can, as noted in the discussion, be explained on the basis of postextrasystolic potentiation and aortic impedance, both of which in the failing left ventricle would tend to increase aortic pressure more so than in the non-failing left ventricle. The mechanism of the response in hypertrophic subaortic stenosis to an extrasystole is somewhat different, being dependent on decreased afterload and probably on postextrasystolic potentiation.

I thank Dr. Eyer for his informative comments.

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Why don t they read the old books?

To the Editor:

Correlation does not necessarily imply causation."[1] With these words Dr Philip R. J Burch started criticizing the risk factor idea in coronary heart disease (*CHD*) in an article which appeared in this JOURNAL in June, 1977 But he did not go far enough in his conclusions, which, in his scholarly treatise, would have meant advocating the dropping of the whole idea of risk factors and instead devoting all energy manpower and financial resources to finding the cause(s) of CHD

Since N Anitschkow in 1913 found cholesterol in atheromata (now for some strange reason called "the plaque") and since John Gofman in 1950 used the then new ultracentrifuge to separate lipoproteins into different layers, cholesterophobia has taken hold of professional and lay people alike and has also laid the groundwork for the accumulation of so-called risk factors for CHD, the number of which has, in the course of time, exceeded 20. This substitution of risk factors for cause(s) of CHD has led to most absurd statements, some of which are still propagated, such as the comparison of London bus drivers with conductors who have to climb stairs, and mail clerks sorting mail a letter carriers, etc. Many of these risk factors have proven t be insignificant, and so we ha e now the division into "major and "minor risk factors. The cholesterol story has taken curious twists and t rns, such as the addition of triglycerides as important indicators of "risk, again largely abandoned since it has been show that exercise, in moderation, 2 to 3 times week, an reduce this danger" just as much as fat reduction ir the diet The "typing of lipoproteins, suggested b F edericksen and Levy has complicated matters as has the recently ad ocated division into DL and LDL h h ha led to the statements that total cholesterol ma not be ndica or t all. Accordingly we are back to Anitschk he f und this substance in atheromata and did not know what t meant Small progress, indeed, in 65 y ar

Purely statistical methods shed no light on causality be it CHD or any other disease since so many people (allegedly about 40 per cent) with CHD have no risk factors whatsoever

The statistical method used to explain causality has been scientifically ttacked by A H T Robb-Smith in his book "The Enigma of Coronary Heart Disease, which gives lucid account of the errors of statistical interpretation. Add to this the finding of myocardial necrosis without coronary artery in ol ement, finding which has recently amazed the medical community and w discover explanatory reports based on experimental evidence in books which have pparently been ignored and/or forgotten

Hans Selye[5] reported on the occurrence of myocardial necroses on the base of hormono-electrolyte imbalances, citing experimental evidence on 30,000 rats. And Wilhelm Raab[6] summarized his lifetime work on catecholamines in an elegantly written book, in which he also cautioned against equating myocardial necrosis with coronary angiopathy Curiously physical exercise recently advocated to increase the HDL/LDL ratio, was recommended by Raab long ago. H also disapproves of statistical methods alone with the following statement. Epidemiological data do not usually contribute much to the nalysis and understanding of basic principles. Indeed, when conclusions drawn from them are geared to fit a prejudicial and outdated terminology with regard to pathogenesis, they are pt to confuse rather than to clarify the issues in question."[6] What we ha to do is abandon the whole concept of risk factors, and devote our energy to finding the cause( ) of myocardial necrosis and of coronary atherosclerosis. Raab and Selye ideas are worth pursuing.

It is not impossible that Raab's catecholamine hypothesis ties in with Friedman and Rosenman s[7] type A and B personality patterns. There may even be genetic basis to the development of these patterns, related to hormonal abnormalities. It is well known that cerebral hemorrhage or tumors may electrocardiographically simulate myocardial ischemia and necrosis. Also worthwhile investigating are the experiments on models by Meyer Texon and others.

But it is about time to "face the facts, as E. and S. R. Corday[11] and others have stated, even if they and we, have to face the resistance of the established trends.

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Reply

To the Editor:

Dr Neurath s scathing remarks about the identification of "risk factors with causal factors on the basis of mere association are, alas, largely justified. However I believe that he is too harsh in his condemnation of "statistical methods

These have an important role in medicine and it is only their *misuse* that has allowed certain enthusiastic epidemiologists and others to make precipitate identifications of causation with association. Most, if not all, techniques of investigation are capable of being misapplied to generate faulty conclusions, but when the rules of statistical inference are strictly observed and the limitations of medical statistics are properly recognized, the risk of serious error should be minimized.

Since writing my Annotation for the JOURNAL I have analyzed wide range of relevant epidemiological data, including statistics for mortality from CHD in England and Wales from 1921 to 1973. By good fortune, the mathematical connections between sex and age-specific death rates and age for the "major risk factors"—smoking, relative weight, hypertension, hypercholesterolemia, lack of exercise, and diabetes—have some very convenient properties. These enable one to circumvent deficiencies in the mortality data that resulted from gross underrecognition of CHD during the earlier part of the period, 1921 to 1973. Consequently the etiological conclusions drawn are probably independent of the temporal changes in diagnosis and classification. My analysis indicates that, for all the above "risk factors," the association with fatal CHD is largely or wholly genetic in origin with little or no causal contribution. What I believe to be the actual causal mechanism, mainly biological in nature, is also described.

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Book reviews

Cardiac Emergencies. Edited by Dean T Mason, Baltimore, 1978, The Williams & Wilkins Company 408 pages. Price $29.50.

This book edited by Mason should interest all physicians. The many contributors have reviewed the field of cardiac emergencies lucidly extensively and very well. Among the many aspects of cardiac emergencies reviewed are cardiac resuscitation, chest pain, pre-hospital coronary care, unstable angina, congestive heart failure and cardiogenic shock, acute pulmonary edema, pulmonary embolism, and other phases of the subject. The approach is the more modern one. Physicians who follow the literature closely and work in large centers will not find anything new among the discussions. Nevertheless, the book is good source for training and for review of the management of cardiac emergencies, an important problem in medicine. Readers will have their own specific differences of opinion, but the approaches and interpretations indicated in *the book are those which prevail at present in the larger* cardiac centers of the USA. This is a well written book on an important subject. Students, housestaff, and all physicians should study this book carefully to learn the present therapeutic practices in the care of cardiac emergencies.

Infective Endocarditis. Edited by Shahbudin H. Rahimtoola, M.D New York, 1977 Grune & Stratton, Inc., 358 pp. Price $31.50.

This is another volume of the series entitled "*Clinical Cardiology Monographs*. The contributors to this volume are numerous and include physicians who have had experience with infective endocarditis The subjects discussed are those of [illegible] to the practicing *physician, internist*, general [illegible] as well as cardiologist It review very well [illegible]hogenesis, pathology clinical features, bacterial and fungal organisms, diagnosis, laboratory diagnosis, and medical and surgical treatment. Infective endocarditis is fairly common and presents important clinical problems which physicians regularly encounter in practice. It offers many complex challenges to the doctor and even to the patient and his family It is disease once almost 100 per cent fatal and now, when recognized early and managed properly it is almost 1[illegible] per cent curable. This is an important disease with [illegible] specific and different problems. This is a good book to [illegible] study on the subject.

Pheochromocytoma. By William Muir Manger and Ray [illegible] Gifford, Jr New York, 1977 *Springer Verlag*, [illegible] pages Price $49.80.

This book represents an exhaustive discussion of [illegible] but interesting, disease. Even though the incidence of pheochromocytoma is rare cause of hypertension, it is an important disease which is readily cured surgically T[illegible] the disease properly not only requires an accurate diagnosis but a thorough knowledge of its pathophysiology by the physicians and surgeons concerned with its management. The authors have thoroughly and clearly reviewed the [illegible] and management of pheochromocytoma. Catecholamine metabolism, pharmacology physiology clinical manifestations, diagnosis, and treatment are discussed. This [illegible] volume provides the reader with the essentials concerning pheochromocytoma. There are over a thousand references in the bibliography for the convenience of those who wish to pursue the subject in greater detail. This [illegible]-page book [illegible] valuable addition to the medical literature. It provides excellent single reference on pheochromocytoma, an extreme-ly interesting disease and exciting to manage.

Books received

Vascularisation et Circulation de l'encephale. By Guy Lazorthes, Andres Gouaze, and Georges Salamon, Paris, New York, Barcelona, Milan, 1978, Masson Publishing Company 214 pages.

Genetics and Counseling in Cardiovascular Diseases. By James J Nora, M.D and Audrey Hart Nora, M.D Springfield, Ill., 1978, Charles C Thomas, Publisher 227 pages. Price $16.00.

Atherosclerosis—Is it reversible? By G. Schettler, E. Stange, and R. W Wissler Berlin, Heidelberg, New York, 1978, Springer Verlag, 104 pages. Price $14.00.

The Heart Attack Handbook. By Joseph S. Alpert, M.D Boston, Toronto, 1978, Little, Brown & Company 139 pages. Price $4.95.

Hypertension Control for Nurses and Other Health Professionals. By Mahendr S. Kochar and Linda M. Daniels, St. Louis, 1978, The C. V Mosby Company 232 pages. Price $10.00.

Intensive Care Radiology: Imaging of the Critically Ill. Edited by Lawrence R. Goodman and Charles E. Putman, St. Louis, 1978, The C. V Mosby Company 363 pages. Price $34.50.

Handbuch der Allgemeinen Pathologie. Edited by H. W von Altmann, F Buchner H. Cottier, E. Grundmann, G. Holle, E. Letterer W Masshoff, H. Meessen, F Roulet, G. Seifert, and G. Seebert, Berlin, 1977 Springer Verlag, 1138 pages.

Zentrale Themen der Sportmedizin. Edited by W von Hollmann, Berlin, 1977 Springer Verlag, 348 pages. Price $16.80.

Management of Hypertension. By K. O'Malley M.D., B.Sc., Ph.D., M.R.C.P (Ed), F.R.C.P.I., E. T O'Brien, M.R.C.P F.R.C.P.I., N. Hickey M.D., M.F.C.M., M.R.C.P.I., and R. Mulcahy M.D F.R.C.P F.R.C.P.I., Dublin, 1978, Irish Heart Foundation, 31 pages.

Announcements

American Board of Internal Medicine Subspecialty Examinations

The next examinations in Hematology, Infectious Disease, Nephrology, Pulmonary Disease, and Rheumatology will be held on June 1, 1980. Registration for these subspecialty examinations will begin on August 1, 1979 and will continue through November 1, 1979. For those who began their residency training in internal medicine *before* June 1, 1970 and who have less than two years of acceptable subspecialty training, this will be the last opportunity for admission to subspecialty examination. Applications for the examination may be obtained from: The American Board of Internal Medicine, University City Science Center, 3624 Market St., Philadelphia, Pa. 19104. Telephone (215) 243-1500.

International Symposium—Pulmonary Circulation III

The International Symposium—Pulmonary Circulation III, will be held in Prague, Czechoslovakia, on July 2 through 4, 1979. The symposium is sponsored by the Societas Europaea Physiologiae Clinicae Respiratoriae and by the European Society of Cardiology. It will be organized and hosted by the Czechoslovak Society for Respiratory Physiology and Pathology and the Czechoslovak Society of Cardiology. For further information, contact: International Symposium Pulmonary Circulation III, Czechoslovak Medical Society J. E. Purkyně, 120 26 Prague 2, Sokolská 31, Czechoslovakia.

[illegible] Conference on Smoking and Health

The fourth World Conference on Smoking and Health will be held in Stockholm, Sweden, on June 18 through 21, 1979. The conference will be organized by the Swedish Ministry of Health and Social Affairs and the National Smoking and Health Association. For further information, contact Dr. Lars M. Ramstrom, Secretary General, RESO Congress Service, Box 23110, S-104 35 Stockholm, Sweden. Telephone (08) 20 16 62.

International Cardiology Conference

The annual International Cardiology Conference, under the patronage of the French Cardiology Society and organized by Drs. J. Facquet, V. Grosgogeat, G. Motte, and J. J. Welti, will take place on May 21 through 23, 1979, at the Faculté de Médecine Pitié-Salpêtrière, 105 Blvd. de l'Hôpital [illegible] Paris, France. For further information, write: Journées Internationales de Cardiologie, Hôpital Fernand-Widal, 200 rue du Fg. Saint-Denis, 75475 Paris Cedex 10, France.

International Society of Mechanocardiography

At the recent World Congress of Cardiology in Tokyo, the International Society of Mechanocardiography was [illegible]. Interested physicians who are active in the field of pulse and sound recordings are invited to apply for membership. [illegible] inquiries to the individuals listed below.

For U.S.A. and Canada: Howard B. Wayne, M.D., [illegible] Sixth Avenue, Suite 203, San Diego, Calif. 92101.

For Mexico, Central and South America: Bernardo L. Fishleder, M.D., Av. Newton 156-402, Mexico City, D.F. Mexico.

For Europe: Hugo Kesteloot, M.D., Dept. of Cardiology, St. Raphael University Hospital, Leuven, Belgium.

For Asia: Tsuguya Sakamoto, M.D., Shinjuku 7-[illegible] Shinjuku-ku, Tokyo 160, Japan.

Canadian Summer Workshop in ECG

The fourth Canadian Summer Workshop in Electrocardiography will be held on July 28 through 31, 1979, at the [illegible] MacDonald, Edmonton, Alberta, Canada. The workshop [illegible] be sponsored by the Rogers Heart Foundation, Inc. For further information, contact: Anne S. Cross, Executive Coordinator, Rogers Heart Foundation, St. Anthony's Hospital, St. Petersburg, Fla. 33705. Telephone (813) 894-0750.

American Heart Journal

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Editorial

Low-dose heparin prophylaxis of venous thrombosis An editorial

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The introduction in Europe of the ¹²⁵I labelled fibrinogen scan of leg veins a decade ago led to documentation that 30 to 40 per cent of all patients with major medical or surgical illness develop thrombotic complications in lower extremity deep veins. Attempts to modify this tendency toward thrombotic complications has led to the introduction of low-dose heparin therapy for the prophylaxis of such venous thrombosis.[1-4] Since the inception of the concept, numerous publications have verified the apparent benefit to patients, the most significant of these reports being the International Multi-Centre Trial, as documented by Kakkar That study appeared to conclusively establish the effectiveness *of low-dose heparin therapy* as its conclusions were drawn from experience with thousands of cases. In fact, it would remain the definitive article on the subject, were it not for certain questions now being raised by several of its participants as to the accuracy of its data.

While the rationale for using low-dose heparin therapy in surgical patients is no doubt valid, its effect is apparently relative. The trauma of operation, the severity of the patient's illness, his immobilization, the presence of cardiovascular instability and of fluid and electrolyte imbalance, are unquestionably factors which increase the clotting tendency and set the stage for thromboembolic complications.[5] When administered early in an appropriate dose, heparin—a potent anticoagulant—should be effective in preventing or modifying this clotting tendency However it is questionable whether a dose of 5 000 units of heparin, administered two or three times daily is sufficient to decrease clotting complications in *all* patients at risk for thromboembolic problems.

The initial studies of low-dose heparin prophylaxis of deep vein thrombosis were carried out in a group of patients being subjected to operations for hip fractures. This is a relatively simple injury *involving a minimal to moderate degree of soft* tissue damage, and the operative procedure used is relatively well standardized. In this group of patients, low-dose heparin prophylaxis of thromboembolism appeared to be particularly effective.

We evaluated the effectiveness of the low-dose heparin regimen on our Trauma Service over a six-month period in two comparable groups of 100 patients each. No significant differences were seen in either the incidence of bleeding complications or in the incidence of clinical thromboembolic complications in the treated versus the control groups. Since the clinical incidence of vein thrombosis and/or pulmonary embolism was 8 per cent, we concluded that the clotting stimulus provided by extensive soft tissue injury shock, transfusion, anesthetics, and immobilization was greater than could be neutralized by the administration of low

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doses of heparin. In fact several patients with clotting complications on our Trauma Service actually had progression of their clotting manifestations despite administration of conventional clinical doses of heparin. Therefore, I am not surprised by the apparent lack of benefit shown for low-dose heparin therapy in some patients, since the clotting tendency varies greatly depending upon the stimulus.[a] At the same time, I could accept the possible benefit of low-dose heparin therapy in some patients with other types of problems whose clotting stimuli were not as intense But the crux of the problem, of course, is the fact that the group of patients showing the highest incidence of clotting complications may benefit the least from low-dose heparin prophylaxis.

A second controversy relating to prophylaxis of deep vein thrombosis centers around the question of whether or not asymptomatic clotting in the veins of the lower leg has, in itself, any serious sequelae. Despite the fact that a high incidence of deep vein thrombosis has been demonstrated by use of ^{125}I labelled fibrinogen scans, the actual clinical significance of these thrombi can be challenged. I have personally not seen any late sequelae of such asymptomatic vein thrombi, nor does the literature document any such sequelae. Disability resulting from deep vein thrombosis relates to its progression to the point of complete obstruction of the deep veins with swelling of the involved extremities from deep venous thrombophlebitis, or to the development of pulmonary embolism. In a small percentage of cases, the former complication may be associated with considerable immediate morbidity and also with the possibility of later development of deep venous insufficiency The most feared complication in these patients, however is the development of pulmonary embolism. This latter complication causes serious immediate morbidity and death. As a result, the principal problem with which the clinician is concerned when venous thrombi occur is preventing pulmonary embolism. I would question whether the clot which is responsible for most of the morbidity comes from these lower leg veins. I rather believe it is more likely that this clot originates in the great veins of the upper third of the thigh and pelvic area which cannot be evaluated adequately with the fibrinogen scan. Consequently I have doubts about the studies which utilize ^{125}I labelled fibrinogen scans to document the effectiveness of prophylactic measures.

The main questions which are raised in relation to the low-dose heparin prophylaxis of deep vein thrombosis, then, are these

1. How does the clinician determine the adequacy of a given dose of heparin in a specific case?

2. Does the prevention of asymptomatic calf vein thrombosis benefit the patient and prevent serious morbidity?

3. Can the fatality rate from pulmonary embolism be modified by the prophylaxis of leg vein thrombosis?

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Clinical communications

ECG pattern of left ventricular hypertrophy in nonobstructive hypertrophic cardiomyopathy The significance of the mid precordial changes

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High QRS voltage, depression of the ST segment, and inversion of the T wave in the left precordial leads are widely accepted to be the electrocardiographic criteria for left ventricular hypertrophy (LVH) Several criteria for the electrocardiographic diagnosis of LVH have been proposed, among which Sokolow and Lyon s criteria have been widely accepted. The greater amplitude of the R wave in Lead V than in Lead V is an adjunct important finding in the diagnosis of LVH Recently the diagnosis and management of hypertrophic cardiomyopathy (HCM) have been given much attention and LVH and ST-T changes were reported to be the most frequent abnormalities in the ECG In a review of the electrocardiograms in 33 patients with nonobstructive HCM, 22 patients were found to satisfy the LVH criteria with the high voltage and ST-T changes involving the midprecordial leads, and showing the most striking abnormal changes in the midprecordial leads in most patients. To our knowledge, there is no documentation concerning ECG description of this midprecordial abnormality The present study was therefore undertaken to discuss the clinical significance of this ECG finding.

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Materials and methods

Twenty three Japanese patients satisfying the conventional ECG criteria for left ventricular hypertrophy—namely high QRS voltage (SV + RV > 35 mm.) coupled with depression of the ST segment and inversion of the T wave in the left precordial leads were selected from reviews of a clinical series of 33 patients with nonobstructive HCM, as defined by Goodwin. Patients with a QRS duration longer than 0.12 sec., and with an abnormal Q wave wider than 0.03 sec. were excluded. The diagnosis of nonobstructive HCM was based on clinical history physical examination, and characteristic echocardiographic findings. Patients with signs of obstruction, i.e., systolic anterior movement of the anterior mitral leaflet in the echocardiogram, pressure gradient in the left ventricular outflow tract, and characteristic angiographic findings[11] were excluded. In 16 patients the diagnosis was also supported by cardiac catheterization and angiographic studies. Standard 12 lead ECGs were recorded with particular attention given to accurate placement of chest electrodes. Half standard and one-fourth standard lead records were also obtained whenever necessary The electric axis in the frontal plane was determined from the conventional methods. The amplitude of the R wave in standard leads and the amplitudes of the R wave and T wave in precordial leads were measured. The sum of the voltage of the S wave in Lead V and the R wave in Lead V was also measured. In addition, the presence or absence of the septal q wave was observed. Vectorcardio-

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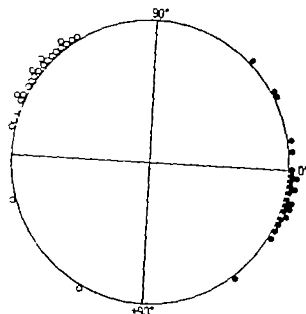


Fig 1 Scattergram depicting the azimuth of the spatial maximal QRS vectors (*closed circles*) and T vectors (*open circles*) Note the location of the maximal QRS vectors anteriorly and to the left and the location of the maximal T vectors posteriorly and to the right.

grams (VCGs) were obtained with patients in the supine position and using the Frank system with the chest electrode placed at the fifth intercostal space The magnitude azimuth, and elevation of the maximum spatial QRS and T vector were calculated as follows

1 The spatial magnitude (SM) according to the Pythagorean theorem

$$SM = \sqrt{x^2 + y^2 + z^2}$$

2. Azimuth (H degrees) according to the formula

$$\tan H \text{ degrees} = \frac{z}{x}$$

3. Elevation (V degrees) according to the formula

$$\cos V \text{ degrees} = \frac{-y}{\sqrt{x^2 + y^2 + z^2}}$$

For elevation, inferior vertical was 0 degrees, superior vertical was +180 degrees Regarding azimuth, horizontal left was 0 degrees, horizontal right was ±180 degrees anterior was +90 degrees, posterior was −90 degree

Results

The pertinent ECG and VCG finding are summarized in Table I A ... f th patient ranged from 23 to 71 years Ther ... les and one female The ECG revealed a ... QRS axis (mean 58.5 degrees) the highest R ... was noted in Lead II in 22 patients (96 per cent) with an R wave greater than 15 mm a ... patients (78 per cent). The QRS complex in aV was not specific, the R wave in aV_L was ... increased. Loss of q wave was noted in Lead I in 20 patients (87 per cent) In 18 patients this was also noted in Lead II and Lead III.

In the precordial leads, the T wave was inverted from V in 22 patients, and from V ... one patient. The ST segment was depressed from Leads V to V in 13 patients and from Leads V ... V in 10 patients. The most striking abnormalities of the QRS-T complex (highest R wave and deepest T wave) were noted in Lead V in ... patients (74 per cent) another three patients ... a deepest T wave in Lead V_4. Loss of q wave was noted in 21 patients in Lead V (91 per cent

In the VCG the magnitude of the spatial QRS vector was increased (> 2.5 mv) in 18 patients (78 per cent) The spatial maximal QRS ... was located anteriorly inferiorly and to the left in 18 patients (78 per cent), and the spatial maximal T vector was located posteriorly and ... the right in 21 patients (91 per cent), superiorly in 17 patients (74 per cent) just discordant with the QRS loop (Fig. 1)

Four representative examples of the ECG ... shown in Fig. 2, and the VCG echocardiogram and angiogram of Case 1 are demonstrated ... Fig. 3.

Case 1 55-year-old male. The ECG (Fig ... showed high QRS voltages in Leads II, III, aV and V through V_6, depression of the ST segment and inversion of the T wave in Leads I, II, III, aV and V through V_6. The electric axis ... degrees. The most remarkable change in the frontal plane was in Lead II in the horizontal plane this was in Lead V_4. Loss of q wa... noted in Leads I, II, III, aV and V_5, V_6. The VCG (Fig. 3A) showed the QRS loop to be located anteriorly inferiorly and to the left ... increased magnitude of the maximum QRS vector The T loop was oriented posteriorly superiorly and to the right just discordant ... the QRS loop. Left ventricular cineangiogram (Fig. 3B) showed a marked hypertrophy of the lower portion of the ventricular septum and the apical area. Selective coronary angiograms (F...

See Hugenholtz et al., J. Electrocardiology ...

Table I Pertinent ECG and VCG data

Case	Age	Sex	Axis	AVL R mm.	I R mm.	I T mm.	II R mm.	II T mm.	III R mm.	III T mm.	V R mm.	V T mm.	V R mm.	V T mm.	V R mm.	V T mm.	V R mm.	V T mm.	V R mm.	V T mm.	SV + RV mm.
1	65	M	73	QS 0	7	−1	25	−2	16	−1	9	+2	28	−10	48	−14	27	−6	17	−2	63
2	56	M	52	qrs 4	10	−3	16	−1	6	+3	6	+1	37	−20	62	−18	28	−4	18	−2	40
3	71	M	60	3	13	−6	22	−1	7	+3	6	+3	20	−12	62	−28	48	−16	30	−6	66
4	29	M	53	qr 7	13	0	16	−2	7	−2	8	+2	36	−8	24	−7	15	−3	13	−2	41
5	68	M	61	qr 3	7	+1	10	−1	5	−1	5	+2	12	−5	40	−10	24	−3	14	−1	42
6	57	M	51	5	12	−4	16	−4	7	+2	2	+5	20	−9	34	−16	32	−12	19	−6	42
7	52	M	64	qr 7	17	−3	38	−4	25	−1	3	+2	22	−8	56	−20	49	−13	38	−8	71
8	29	M	71	rs 1	15	−7	48	−14	36	−6	17	+5	60	−19	73	−18	60	−16	40	−12	82
9	37	M	73	QS 0	6	−3	23	−3	17	−2	3	+3	28	−14	29	−16	23	−6	17	−5	53
10	30	F	85	rs 4	4	−1	47	−5	45	−3	15	−1	34	−6	39	−8	20	−4	25	−3	49
11	51	M	30	qr 8	12	−1	12	+2	2	+3	1	+1	23	−11	30	−11	29	−5	18	−1	39
12	29	M	30	qrs 5	12	−7	11	−4	3	+2	11	+3	26	−10	32	−14	30	−14	19	−8	44
13	41	M	49	qr 2	8	−2	11	−4	4	−2	1	+4	21	−12	30	−15	26	−8	11	−3	42
14	54	M	69	rsr 5	14	−1	23	−2	13	−1	4	+2	21	−12	45	−14	37	−9	26	−4	65
15	52	M	60	rs 1	13	−2	25	−1	11	0	4	+1	28	−8	61	−13	40	−6	24	−2	59
16	54	M	44	qr 2	6	−1	12	−2	2	−1	1	+7	20	−2	46	−20	32	−14	19	−4	46
17	50	M	78	QS 0	5	−2	17	−4	13	−2	1	+5	14	−12	42	−24	40	−18	24	−7	57
18	39	M	40	qr 8	17	−2	21	−3	6	−1	2	+2	24	−4	43	−18	46	−16	29	−6	63
19	27	M	78	rs 3	8	−3	28	−3	26	−2	7	+3	28	−7	29	−14	30	−9	22	−5	52
20	59	M	77	rs 1	8	−2	31	−2	23	0	11	+4	30	−3	28	−8	43	−7	30	−3	65
21	65	M	67	rs 2	9	−3	21	−1	11	+2	3	+3	12	−1	19	−5	38	−9	25	−4	49
22	41	M	62	qr 2	9	−1	18	−2	10	−1	2	+3	12	−2	20	−4	25	−6	17	−3	63
23	22	M	60	qr 2	11	−1	17	0	6	+1	11	+6	23	+8	29	−1	28	−5	21	−4	49

Case	Leads of ST depression	Leads of loss of q wave	Spatial max QRS Mag. mv.	Spatial max QRS Azi*	Spatial max QRS Ele.	Spatial Max T Mag mv.	Spatial Max T Azi.	Spatial Max T Ele.
1	I V$_{3-6}$	I II III F V$_{3-6}$	2.65	−30.0	48.0	0.67	−128.9	96.1
2	I II III L F V$_{4-6}$	I II III L F V$_{4-6}$	3.22	13.6	70.1	1.27	−137.9	84.6
3	I L V	I II III L F V	3.40	12.8	72.5	1.17	−162.1	85.6
4	I II III F V$_{4-6}$	I V	1.88	80.0	56.2	0.56	−138.5	112.0
5	I II V	II III F V$_{4-6}$	2.14	3.6	72.6	0.28	−135.0	94.4
6	I II L V$_{4-6}$	I II III L F V$_{4-6}$	2.41	17.1	64.4	0.80	−152.1	100.1
7	I II III F V	I II III F V$_{3-6}$	6.34	−32.3	30.5	1.19	−148.3	133.6
8	I II III F V	I II III F V	6.27	8.8	25.3	1.48	−140.2	127.5
9	I II V$_{4-6}$	I II III F V$_{4-6}$	3.09	0	50.4	1.49	−134.7	92.3
10	I II III F V	I L V	6.51	24.5	16.2	0.74	−131.3	90.3
11	I L V	I II III F V$_{4-6}$	3.45	21.2	74.2	0.79	−139.2	76.1
12	I II L F V$_{4-6}$	I II III F V$_{4-6}$	2.36	22.4	67.7	0.80	−157.7	97.9
13	I II III F V	I II III F V$_{3-6}$	2.14	2.0	66.6	0.88	−156.9	109.9
14	I II III F V	I L V	2.31	−7.4	56.8	0.72	−128.6	107.0
15	I II L V	I II III L F V	4.21	12.6	48.6	0.68	−125.3	97.6
16	I II F V	I II III F V$_{4-6}$	2.10	18.6	60.0	1.06	−144.7	98.8
1	I V	I II III F V$_{4-6}$	2.37	3.2	51.9	1.22	−147.1	104.2
18	I II III F V	I II III F V$_{4-6}$	2.80	9.9	65.5	0.87	−158.3	104.6
19	I II L F V$_{4-6}$	L	4.12	8.3	27.0	1.09	−151.4	109.8
20	I II III F V	I L V	2.31	15.2	47.4	0.60	−168.5	96.6
21	I L V$_{4-6}$	I II III L F V	2.97	6.1	56.3	0.58	−167.9	84.1
22	I II F V	I II III F	2.80	−48.0	62.8	0.78	+162.1	102.3
23	I II L V$_{4-6}$	II III F V	2.11	−12.2	62.2	0.57	+117.0	88.0

† Abbreviations: Mag = magnitude; Azi. = azimuth, Ele. = elevation.

CASE 1 · CASE 2 · CASE 3 · CASE 4

Fig. 2. Four examples of the ECG showing the remarkable QRS-T changes in midprecordial leads and in Lead II. The electric axis was normal. The QRS complex in aV was QS, qr or r pattern without the increase in voltage of aV

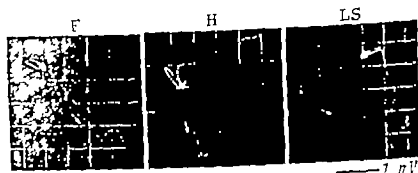


Fig. 3A. Case 1. Vectorcardiogram showing large QRS loop oriented anteriorly and to the left. The T loop is oriented posteriorly, superiorly and to the right, discordant with the QRS loop.

3C) showed normal right and left coronary arteries without significant obstruction. The echocardiogram (Fig. 3D) showed the hypertrophic interventricular septum and the normal thickness of the posterobasal left ventricular wall.

Discussion

Increased magnitude and rotation of the QRS vector toward the effective electrical site of the hypertrophied ventricle and rotation of the T vectors away from the QRS vector have been considered to be the electrical effects of ventricular hypertrophy. The increased magnitude of the QRS wave, depression of the ST segment, and inversion of the T wave in the left precordial leads indicate left ventricular hypertrophy. Factors responsible for the increased magnitude of the forces being generated by the hypertrophied ventricle are generally considered as follows: (1) decreased internal resistance of the muscle fiber and an increased current flow in the conducting medium, (2) increased surface area and greater



Fig. 2. B and C. Case 1. *B*, Left ventriculograms (right anterior view; upper, end-diastole; lower, end-systole) showing the thickening of the lower portion of the interventricular septum and apical area. *C*, Selective coronary angiograms (upper, left coronary artery, right anterior oblique view; lower, right coronary artery, left anterior oblique view) showing the normal coronary arteries.

thickness of the wall of the hypertrophied ventricle with tangential spread of activation wave through the wall of the hypertrophied ventricle, and (3) closer proximity of the heart to the chest wall.

Although the hypertrophy is usually diffuse and symmetric, localized hypertrophy may also develop in certain types of overload. There is a good theoretical reason to postulate that the localized hypertrophy can also be associated with an increased magnitude in the QRS force and rotation of the QRS force to the hypertrophied area, the configuration of electrocardiogram and vectorcardiogram then being influenced greatly by this vector. In the right ventricle, the rsR′ pattern in Lead V observed in atrial septal defect was considered to be a manifestation of localized hypertrophy of the crista supraventricularis, the deep S waves in Leads V through V were interpreted to mean the hypertrophy of the inflow tract of the right ventricle, and the tall R wave in Lead V was considered to be a concentric hypertrophy of the right ventricle frequently observed in pulmonary stenosis. In the left ventricle, the hypertrophy of the posterobasal region of the left ventricle had been postulated to explain the dominance of right posterior forces observed in patients with supraventricular aortic stenosis and coarctation of the aorta. The VCG differences between the outflow overload in aortic regurgitation and inflow overload in mitral regurgitation have also been discussed.[14]

Recently hypertrophic cardiomyopathy has received much attention clinically. HCM was defined by Goodwin to be a massive muscular hypertrophy especially concentrated at the region of the ventricular septum in contrast to the symmetric concentric hypertrophy secondary

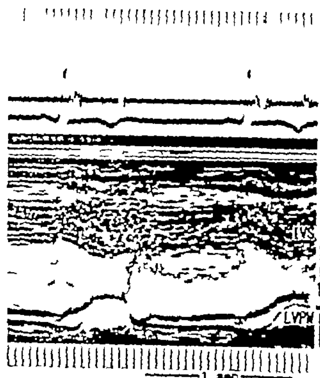


Fig. 3D Case 1 Echocardiogram showing the marked thickening of the interventricular septum and normal thickness of the posterobasal left ventricular wall.

to the pressure overload of the left ventricle. The asymmetric septal hypertrophy has been demonstrated by necropsy and echocardiography. Two forms of HCM have been classified according to the presence or absence of outflow obstruction. The obstructive form is considered identical to idiopathic hypertrophic subaortic stenosis. The nonobstructive form is not so rare, and is encountered more often in Japan than is the obstructive form.

The difference in the distribution of hypertrophy in patients with nonobstructive and obstructive HCM have been recently reported in echocardiographic angiographic and pathological studies. The lower to upper septal ratio was significantly greater in the n obstructive form, and in the nonobstructive f rm the free wall behind the post r mitral leafl t is not thickened however the free wall ... the posterior leaflet was thick ned ... th absence of the normal decrease in w ll th k ... f om base to apex In patients w th ... e form the free wall of the left ... thick ned with a progressively decreased ... f m base to apex and this is identical ... ding seen in

patients with valvular aortic stenosis or systemic hypertension.

The ECG in hypertrophic cardiomyopathy is abnormal in almost every case. Left ventricular hypertrophy with ST-T changes, abnormal Q waves, and conduction disturbance are the most frequent abnormal findings, and this has been reported mainly in studies of the obstructive form. Abnormal Q waves with upright T wave in the inferior and left precordial leads have been reported as findings suggestive of obstructive HCM. Other findings have not been reported as being specific for HCM. The R wave in Leads V and V has been considered to be influenced by the proximity of the spread of the excitation wave in the lower portion of the septum toward the electrode. Therefore the R wave in Lead V is usually greater than that in Lead V in normal individuals from the standpoint of this proximity effect, but usually there were no ST or T abnormalities in this nature. The location of the chest leads may affect the voltage of the precordial leads, the voltage becoming abnormally high or low depending on placement of the electrodes. Special attention has been given to this point. Regarding malplacement of the electrodes, the association of the depression of the ST segment and inversion of the T wave in the present series made it impossible to interpret the tall R wave in Leads V and V as malplacement of the electrodes. In the VCG the QRS loop was located anteriorly and to the left, in contrast to the concentric left ventricular hypertrophy which was located posteriorly and to the left.

Contrary to previously reported data on LVH that most of these patients have a horizontal heart position and a tendency to left axis deviation (though true left axis deviation is rare), it is interesting that the electric axis in the present study was around 60 degrees in the so-called semivertical heart position.

Accompanying right ventricular overload, either secondary to left ventricular overload or an associated independent lesion, was one possible explanation for the atypical electric heart position in LVH. In our series there were no patients with heart failure, or associated with right-sided heart disease.

Echocardiograms showed a markedly hypertrophic interventricular septum in all patients with a progressive increase in thickness toward

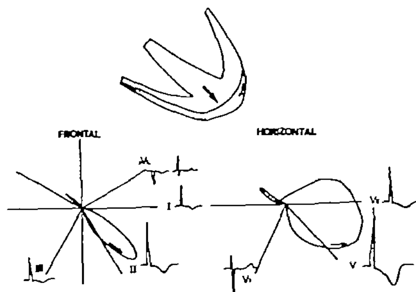


Fig. 4. Diagram to show the increase in electromotive forces from the lower portion of the septum and apical area which pull the QRS vector anteriorly inferiorly and to the left, and revealing the most remarkable abnormalities in Lead II and in the midprecordial leads.

the lower portion. The posterobasal left ventricular wall was not hypertrophied. Angiography performed in 16 patients showed a hypertrophied ventricular wall and/or papillary muscle in the lower portion of the septum and apical area in 14 patients.

The increased electromotive force from the asymmetric septal hypertrophy especially the lower portion and apical area, may thus pull the QRS forces anteriorly inferiorly and to the left, thus producing the most remarkable abnormalities in Leads II, the midprecordial leads, a normal to semivertical heart position in the ECG, and a prominent left anterior QRS loop in the VCG (Fig. 4)

The T waves were most deeply inverted in the midprecordial leads where the R waves were also the highest. In the VCG the T loops deviated posteriorly and to the right just discordant with the QRS loops (Fig. 1) In 16 cases of selective cineangiography a normal coronary artery without significant obstruction was noted. Giant negative T waves were also reported by Yamaguchi and associates[11] in a series of hypertrophic cardiomyopathy These findings suggested that the T waves might be secondary to the result of reversed order of repolarization from the hypertrophic lower septum and apical area. Although the relative myocardial ischemia from the decrease in the number of capillaries per unit volume of the myocardium may also be another factor related to T wave change, the true coronary artery disease is not the cause of the deeply inverted T wave such as seen in other instances of the deeply inverted T wave in the midprecordial leads.[18]

Loss of q waves in Leads I, V_5, and V in the ECG have been noted frequently in left ventricular hypertrophy and this was considered to be a finding of so-called systolic overload pattern secondary to aortic stenosis or systemic hypertension. This was also noted in the present series. The mechanism involved in the loss of q wave has been the subject of discussion in the literature. Incomplete left bundle branch block or block of the septal division of the left bundle branch[17] had been proposed. Burch and DePasquale[18] reported that in 80 per cent of the autopsy verified septal fibrosis there had been an absence of septal q wave in Leads I, aV_L, V_5, and V Failure of the early activation of the septum due to electrically inactive fibrous tissue, with the electrical activation initially activated from the apex, was proposed as the explanation. Though the septal theory of loss of q wave cannot be ruled out, increased electrical activity in cases of asymmet

ric septal hypertrophy particularly in the lower portion may be involved from the beginning of ventricular activation and may lead to the loss of q waves.

It is concluded that the ECG pattern satisfying the diagnostic criteria for LVH with the most remarkable changes noted in the midprecordial leads, Lead II with a normal QRS axis, is characteristic for nonobstructive HCM. The pathological correlation is now being investigated.

Summary

A review of electrocardiograms from 33 patients with nonobstructive hypertrophic cardiomyopathy was made. In 22 patients there was noted a high QRS voltage depression of the ST segment and inversion of the T wave, satisfying the diagnostic criteria of left ventricular hypertrophy with the abnormal changes not only extending to the midprecordial leads but showing the most striking abnormal changes in Lead V in 20 patients. The frontal plane electrical axis was normal (around 60 degrees) with the most remarkable changes in Lead II. In the VCG the magnitude of the QRS loop was increased and directed anteriorly and to the left, and the T loop was deviated posteriorly and to the right opposite the QRS loop. The asymmetric septal and apical hypertrophy was noted on echocardiography and/or angiocardiography. The coronary arteries were normal without significant obstruction in selective coronary angiography. It was postulated that the asymmetric septal and apical hypertrophy was reflected in this ECG pattern. The recognition of this ECG pattern provides pertinent information in the clinical detection of nonobstructive HCM.

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Thrombosis of epicardial coronary veins in acute myocardial infarction

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The incidence, cause and significance—if any—of thrombosis of epicardial coronary veins in patients with AMI is unknown. Venous thrombosis is related to increased platelet aggregation which is known to occur in various forms of stress and after tissue damage. Increased platelet aggregation is found in patients with coronary artery disease and AMI.

Involvement of platelets is an initial event in the formation of thrombi and early thrombi may consist purely of platelets. Thrombosis of epicardial coronary arteries in AMI has been described in innumerable papers whereas pathological changes in epicardial coronary veins have almost escaped notice.

The purpose of this paper is to draw attention to the presence of thrombosis of epicardial coronary veins in cases of AMI and to evaluate some factors of importance to the development of such thrombi.

Material and methods

In a consecutive autopsy series of 63 patients with clinically definite or possible AMI it was found that 32 had transmural and 16 had subendocardial AMI. Two had recent occlusive coronary artery thrombosis but both survived too briefly—less than 8 hours—for postmortem demonstration of AMI. These 50 patients are the material for this study.

The autopsy technique has been described previously. It includes a meticulous histological examination of cross-sectioned epicardial coronary vessels. The patho-anatomic diagnosis of AMI is based on naked eye findings, Nitro-BT test, and light microscopy. The AMI is quantitated by the point-counting technique and is recorded in per cent of ventricular mass. A transmural AMI extends through more than the inner half of the ventricular wall, and a subendocardial AMI is limited to the inner half of the wall. Combined AMI's are transmural with additional subendocardial extension.

Arterial and venous thrombosis is defined as occlusion of the vessel lumen by admixture of platelets, fibrin, leukocytes and erythrocytes set in a laminated arrangement, i.e., lines of Zahn. In the arteries (Fig. 1) the thrombi are adherent to the luminal surface and atheromatosis is present. In the veins (Fig. 2) no structural changes are demonstrated in the vessel wall. The venous thrombi appear to be of more recent date than the arterial thrombi: the relative amount of platelets is higher, they are looser in texture, and they show more pronounced shrinkage due to fixation. Thus venous thrombi often appear as "freely floating" but attachment to the vessel wall can be demonstrated.

Statistical evaluation is performed by Fisher's and Mann Whitney's test.

Results

In 16 of 50 cases thrombosis of epicardial coronary veins was demonstrated.

Five patients had aortic and one had mitral valve stenosis. In all six cases venous thrombosis was demonstrated (Table I). Three had transmural and two had subendocardial AMI, and one had recent arterial thrombosis.

Of the 44 patients without valvular heart

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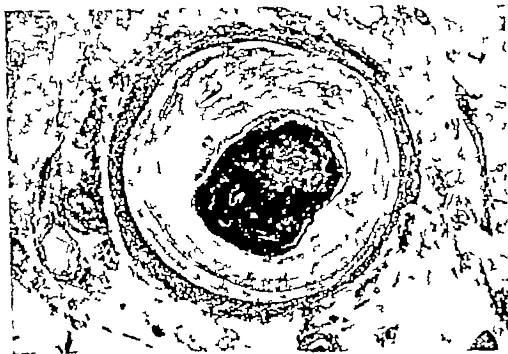


Fig. 1 Cross-section of epicardial coronary artery showing atheromatosis and occlusion by thrombus adherent to luminal surface. (Verhoeff elastica- an Gieson stain, original magnification ×16).

disease (Table I) 10 with transmural AMI involving at least 30 per cent of the left ventricular mass had venous thrombosis, and six of these had very large AMI's involving at least 70 per cent of the left ventricle. None of the seven patients with transmural AMI less than 30 per cent and none of the 14 patients with subendocardial AMI had venous thrombosis. There is no statistical difference in the size of AMI between transmural AMI s less than 30 per cent and subendocardial AMI's. Thus venous thrombosis was demonstrated in 10 of 22 cases with large and in none of 22 cases with small AMI's ($p < 0.002$).

Mean post-attack survival time in patients with transmural AMI without valvular heart disease was the same in patients with (7.2 days, N = 10) as in patients without venous thrombosis (7.0 days, N = 19) However none of the nine patients who died within 24 hours after the acute admission had venous thrombosis, while 10 of the remaining 20 patients had venous thrombosis ($p < 0.002$).

Among the 44 patients no statistically significant difference was found in the incidence and severity of coronary artery disease between those with and those without venous thrombosis. At least 75 per cent stenosis of 1 main artery was found in 10 patients (100 per cent) with, and in 33 of 34 patients (94 per cent) without venous thrombosis. At least 75 per cent stenosis of two or three main arteries was found in 60 per cent and 82 per cent, respectively

Localization of venous thrombosis in relation to arterial thrombosis and to type of left ventricular AMI appears in Table II. Arterial thrombosis was seen in 12 of 15 cases of AMI and was in all cases localized to the arteries supplying the infarcted area. Three AMI's were non-thrombotic and they all had aortic valve stenosis. In all 15 cases of AMI the venous thrombi were localized to veins draining the infarcted myocardium. In case No. 6 the vein accompanying the circumflex artery was thrombosed but the anteroseptal AMI also involved the marginal wall in the apical part of the left ventricle. In case No. 29 the circumflex artery continued as a posterior descending artery In seven cases there was thrombosis of two coronary veins in four of these cases both veins drained infarcted myocardium, and in another three cases one of the veins drained an area without demonstrable AMI. Two of these latter patients died in cardiogenic shock.

In all, 12 of 50 patients died in cardiogenic shock. Seven had transmural and four had suben

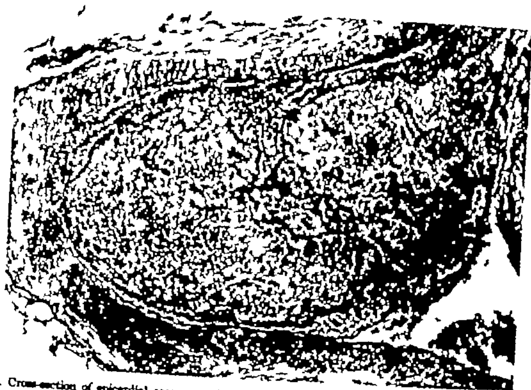


Fig. 2. Cross-section of epicardial coronary vein occluded by thrombus showing lines of Zahn. There are no structural changes in the vessel wall. (Hematoxylin and eosin stain, original magnification ×80).

Table 1 Thrombosis of epicardial coronary veins in relation to valvular heart disease and to type and size of left ventricular AMI

	No. of cases	Venous thrombosis	
		With	Without
Valvular heart disease absent			
Transmural AMI			
> 30%	2	2	
< 30%	1	1	
Subendocardial AMI	2	2	
Recent arterial thrombosis	1	1	
Total	6	6	
Valvular heart disease present			
Transmural AMI			
≥ 70%	6	6	
30-70%	16	4	12
< 30%	7		7
Subendocardial AMI	14		14
Recent arterial thrombosis	1		1
Total	44	10	34

docardial AMIs and one had recent thrombosis without demonstrable AMI. Five of 16 patients with venous thrombosis and seven of 34 patients without venous thrombosis died in cardiogenic shock ($p > 0.2$).

Myocardial rupture was seen in four of 10 cases of transmural AMI with, and in three of 13 transmural AMIs without venous thrombosis ($p > 0.2$). There was no statistically significant difference in heart weight between the two groups.

During their stay in hospital four of 16 patients with venous thrombosis were in the therapeutic level on anticoagulant medication compared to four of 34 patients without venous thrombosis ($p > 0.2$).

Discussion

The patho-anatomic diagnosis of very early AMI is difficult. Light microscopy has little to offer since specific changes will not be visible until after at least 12 hours.[1] Demonstration of loss of dehydrogenases in the infarcted myocardium (Nitro-BT test) will reveal AMI's of 6 to 8 hours duration. It has been suggested that the presence of wavy muscle fibers[3] should indicate very early (1 hour duration) AMI but this phenomenon remains to be clarified and has not been applied in this study.

Rigid criteria must be applied to avoid confusion of true thrombi with postmortem clots which are composed of the normal elements of the blood in more or less normal proportions. The formation of true thrombi require circulating blood [illegible]

Table II Localization of venous thrombosis in relation to arterial thrombosis and to type of left ventricular AMI

Patient No.	*Thrombosis of*		*Type of left ventricular AMI*	*Combining manifestation*
	Coronary veins	*Coronary arteries*		
43	LAD	LAD	Antero-septal	
9	DXT LAD	LAD	– –	External rupture
39	DXT LAD	LAD	– –	
6	FX	LAD	– –	Internal rupture
38	DXT LAD		Combined anterior	Aortic stenosis
46	DXT	DXT	Inferior	Mitral stenosis
29	LAD, FX		Combined inferior	Aortic stenosis
14	DXT	DXT	Subtotal†	Internal rupture
4	LAD, FX	LAD	– –	Internal rupture
34	LAD	LAD	– –	
44	LAD	LAD	– –	
62	DXT	DXT LAD	– –	
68	LAD, FX	LAD	– –	
54	DXT FX	DXT	Posterior papillary muscle	Aortic stenosis
53	DXT		Postero-septal subendocardial	Aortic stenosis
23	LAD FX	DXT LAD		Aortic stenosis

DXT: right coronary artery. LAD: left anterior descending artery. FX: left circumflex artery. The veins are named by the arteries they accompany.
†Transmural AMI of anterior and posterior wall and of interventricular septum involving $\gtrsim$ 70% of ventricular mass.

and the ratio of formed elements is totally out of proportion to that in circulating blood. Early arterial thrombi may be composed purely of platelets[14] and involvement of platelets was shown by Erhardt and associates[4] to be an initial event.

The demonstrated high incidence of venous thrombosis in large AMI's is probably due to the pronounced tissue damage. Gjesdal and Sørlie, in their experimental study on regional ischemia during vascular surgery found that increased platelet aggregation was related to metabolites from the ischemia area, especially platelet factor 4, and to duration of the ischemic period. This is in agreement with the findings in this study where venous thrombosis was found in veins draining large infarctions and only in patients surviving the acute attack for more than 24 hours.

Jørgensen found that infusion of ADP resulted in platelet aggregation and that these were formed in the flowing blood independent of the vessel wall, as also demonstrated in this study. In patients with valvular heart disease, damage to the platelets with resulting ADP release might explain the formation of venous thrombi.

It was previously suggested by us[1] that thrombosis of coronary veins might explain *false-negative* Nitro-BT tests seen in large AMI's and in cases with myocardial rupture. In this series with four cases of false-negative Nitro-BT tests, two had venous thrombosis and two had myocardial rupture, but in the remaining 14 cases of venous thrombosis and in five cases of myocardial rupture the Nitro-BT test was clear-cut and in agreement with naked eye findings and/or light microscopy. Thus venous thrombosis does not explain the false-negative Nitro-BT tests.

Incidence and severity of coronary artery disease, heart weight, anticoagulant medication, and cardiogenic shock seem to be of no importance to the development of coronary vein thrombosis.

Summary

Thrombosis of epicardial coronary veins was demonstrated in 16 of 50 cases of left ventricular acute myocardial infarction and/or recent coronary arterial thrombosis. All patients with valvular heart disease had venous thrombosis. In cases without valvular heart disease, venous thrombosis was seen in infarctions involving more than 30 per cent of the left ventricular myocardial mass with a post-attack survival time of at least 24 hours. The veins thrombosed were in all cases

those draining the infarcted myocardium. Coronary vein thrombosis seems not to be prevented by anticoagulant medication

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Sarcoidosis of the cardiac conducting system

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Between 10 and 20 per cent of cases of sarcoidosis submitted to autopsy disclose cardiac involvement. The lesions involve mainly the myocardium and the endocardium, rarely the epicardium. Several authors have described lesions of the conducting system. In most cases the lesions have been confined to the atrioventricular node and the bundle branches. Only one case of cardiac sarcoidosis claiming sinus node involvement has been published. The main purpose of the present report is to describe a case with sarcoid lesions of the conducting system where the major part of the sinus node was replaced and where the left bundle branch was interrupted by granulomatous tissue.

Material and methods

Among 2,960 consecutive, routine autopsies performed at the Department of Pathology Aker Hospital, from 1973 until 1976, evidence of sarcoidosis was found in 13, of which six had been diagnosed during life. In nine cases the autopsy included histological examination of the conducting system, using a modified version of Hudson's technique. Six blocks from the sinus node region and six blocks from the septal region, including the atrioventricular node and bundle of His, were embedded in paraffin and sectioned for histological examination together with an additional number of blocks (1-6) taken from the myocardium. The sections were stained routinely with hematoxylin and eosin.

Results

The main findings of the series are summarized in Table I. Sarcoid lesions of the heart were found in two cases, which are described below

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Case No. 1 (Table I) The patient was female, aged 52, and had been hospitalized for acute pyelonephritis several years previously. During the last few years she had been treated for hypertension. She had a normal chest x ray in 1971. Since 1972 she had complained of chest pain and was treated with nitroglycerin for assumed angina pectoris. After sudden collapse on January 14, 1973, she was admitted to Aker Hospital. On arrival the ECG showed asystole, there was no spontaneous respiration, and she had dilated pupils. Resuscitation was attempted, but was unsuccessful.

Autopsy findings. The heart weighed 340 Gm. and was well contracted. The coronary arteries were mostly free from atherosclerotic lesions and were without severe stenosis or occlusions. The valvular apparatus and the myocardium appeared grossly normal, without visible scars or fibrosis. The lungs weighed 1160 Gm. Grayish white firm nodules with diameters of 2 to 10 mm. were found in the lungs, in enlarged mediastinal lymph nodes, and in the spleen.

Microscopical examination. Histological examination revealed sarcoid granulomas in the heart, lungs, liver spleen, lymph nodes, and in the bone marrow. The granulomatous lesions had a similar histological appearance in the various organs and showed both discrete and confluent lesions composed of epithelioid cells and Langhans-type giant cells with occasional asteroid bodies. The granulomas were surrounded by lymphocytes and some fibrocytes. Caseous necrosis, fibrosis, and hyalinization were not seen. Special stains for fungi and bacteria, including acid fast bacilli, were negative.

Sections of the myocardium taken from the interventricular septum showed sarcoid granulomas, whereas no pathological lesions were found in the anterior wall of the left ventricle, the papillary muscles, and the right ventricle. Six sections from the sinus node region showed nearly

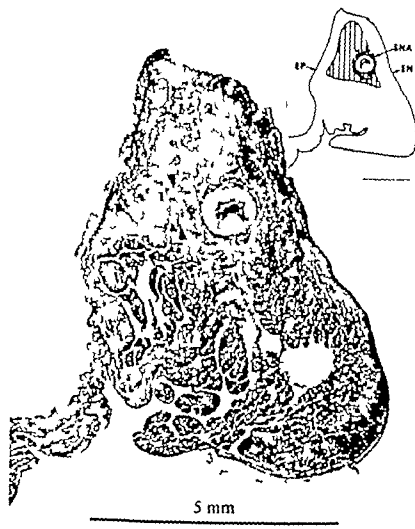


Fig 1A Microphotograph of sinus node sarcoid lesion. The sinus node region *(dotted area)* is nearly completely replaced by sarcoid granulomatous tissue *(hatched area)*. Transverse section of the sinus node artery (SNA). EN endocardium of the crista terminalis. *EP* uninvolved epicardium over sinus node region. (Original magnification ×1 Hematoxylin-eosin stain.)

complete replacement of the pacemaker fibers by confluent granulomatous tissue (Figs. 1A and 1B) sparing only a few fibers close to the sinus node artery (Fig. 1C). Granulomas were found also in the adjacent atrial myocardium and close to nerves in the subepicardial fat. One of the six sections from the cardiac septal region showed a subendocardial, nodular mass of granulomatous tissue which interrupted fibers of the left bundle branch (Figs. 2A and 2B). The atrioventricular node, the bundle of His, and the right bundle branch were all free from sarcoid lesions.

Case No. 7 (Table I) The patient was female aged 71 and had been hospitalized for rheumatic heart disease in 1971. On September 27 1975, she was admitted to Aker Hospital with symptoms of acute myocardial infarction. Blood pressure was 70 pulse rate 100/min. Cardiac arrhythmias were not noted. She died shortly after admission from cardiac failure.

Autopsy findings. The heart weighed 430 Gm and showed valvular aortic stenosis and hypertrophy of the left ventricular wall. The coronary arteries were severely stenotic due to atherosclerosis. Grossly the myocardium appeared normal but histological examination demonstrated small foci of early myocardial necrosis. Small grayish white nodules with an average diameter of 1 mm were found in the mediastinal lymph nodes. Histological examination showed sarcoid granulomas in the myocardium, lungs, liver, spleen, and lymph nodes. The lesions were mostly hyalinized but occasional epithelioid cells, Langhans-type giant cells, and lymphocytes were seen.

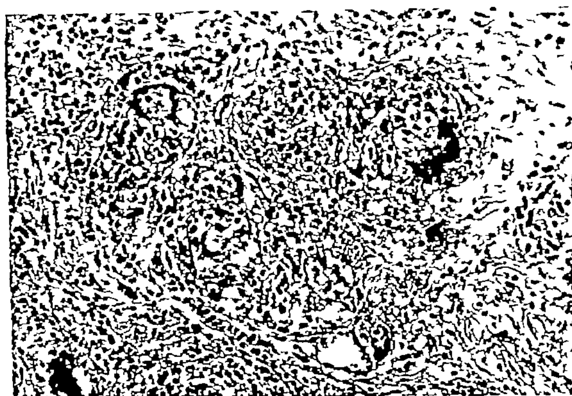


Fig. 1B. Detail from *Fig. 1A* (*arrowheads*). Florid sarcoid granuloma from the sinus node lesion. Note multiple giant and epithelioid cells. (Original magnification ×25).



Fig. 1C. Detail from *Fig. 1A*. A few intact pacemaker fibers (*arrows*) are seen outside the lower part of sinus node artery (*upper right*). (Original magnification ×25.)

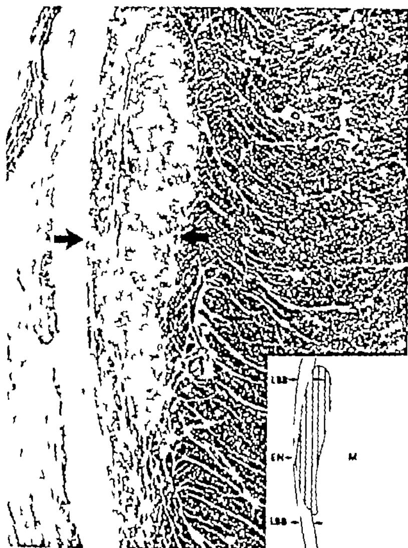


Fig 2A Microphotograph of the left side of the interventricular septum. The left bundle branch interrupted by sarcoid granulomatous lesion *(hatched area)*. *LBB*, left bundle branch, *EN* endocardium of left ventricle; *M*, myocardium (Original magnification ×2.8. Hematoxylin-eosin stain.)

Sections taken from the interventricular septum and from the sinus node region revealed small subendocardial sarcoid granulomas. The lesions were localized adjacent to the bundle of His and to the sinus node but there was no direct damage to these structures.

Discussion

In the present autopsy series cardiac involvement was found in two of 13 cases of sarcoidosis. This is in agreement with previous reports stating cardiac involvement in up to 20 per cent in similar series.[4] Despite the presence of pulmonary involvement in all of our 13 cases only six had been diagnosed during life (T 1 I). In three cases death was attributed t th p ll ionary sarcoidosis with chronic cor pulmonale. One patient also had a pulmonary aspergilloma (case No. 12, Table I) and another had a lung abscess (case No. 13, Table I).

In the literature we have not been able to find more than one report claiming demonstration of sarcoid involvement of the sinus node. In 1971 Gozo and colleagues reported two cases with sarcoid involvement of the heart, one of which at autopsy showed that "the areas of S-A and A-V node were extensively involved by granulomatous tissue and fibrosis." However the method used for examination of the cardiac conducting system is not described The authors point out that the nodal architecture could not be identified and there is no mention of the sinus node artery as a

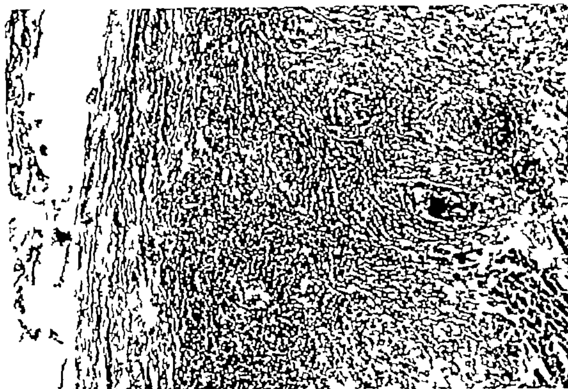


Fig. 2B. Detail from region shown in *Fig. 2A (arrowheads)*. Sarcoid granuloma with prominent giant cell and lymphocytes. (Original magnification ×10.)

Table I Presence of sarcoid lesion

Case	*Age*	*Sex*	*Clinically diagnosed*	*Myocardium*	*Cardiac conducting system*	*Lung*	*Liver*	*Spleen*	*LN*	*Bone marrow*	*Cause of death*
1	62	F	N	+	SN, LBB	+	+	+	+	+	Sarcoid cardiac lesion
2	36	M	N	–	Not examined	+	+	+	+	+	Suicide
3	68	F	Yes	–	–	+	–	+	+	+	Sarcoidosis with chronic cor pulmonale
4	61	F	N	–	–	+	+	+	+	–	Cerebral hemorrhage
5	67	M	Yes	–	–	+	+	+	+	+	Cerebral hemorrhage, Pulmonary embolism
6	87	F	No	–	Not examined	+	+	–	–	–	Severe coronary atherosclerosis
7	71	F	No	+	Adjacent to SN	+	+	+	+	–	Atherosclerotic heart disease
8	68	F	N	–	Not examined	+	+	–	–	–	Myocardial infarction
9	64	F	Yes	–	–	+	–	+	+	–	Sarcoidosis with chronic cor pulmonale
10	69	M	Yes	–	–	+	–	–	–		Chronic interstitial nephritis with uremia
11	96	M	N		Not examined	+	–				Atherosclerosis with gangrene of lower extremities
12	65	F	Yes	–	–	+	+	+	+		Sarcoidosis and pulmonary aspergilloma
13	52	F	Yes	–	–	+	–	+	+	–	Sarcoidosis with chronic cor pulmonale, Lung abscess

Abbreviations: LN, lymph nodes, SN, sinus node, LBB, left bundle branch.

important hallmark in identifying the sinus node region ECG showed second degree AV block, but there was no mention of atrial arrhythmia. It may therefore be seriously doubted if the sinus node really had been identified and was severely damaged in this case.

Clinical information about our patient with sarcoid involvement of the cardiac conducting system (Case No 1, Table I) is incomplete. She had been treated for hypertension and for assumed angina pectoris. At autopsy however neither left ventricular hypertrophy nor evidence of coronary artery disease were found. The reason for her chest pain is obscure. The sarcoid lesions of the myocardium were small and can hardly explain the chest pain. Symptoms related to cardiac arrhythmia had not been noted and to our knowledge no ECG had been taken until her last admission. In general her sarcoid lesions appeared florid without signs of older lesions (fibrosis or hyalinization) This may indicate a fairly rapid development of the lesions, and might explain the negative history of previous cardiac arrhythmia. As to her final illness, the autopsy findings suggest that the patient's sudden death is related to the sarcoid cardiac involvement. One [illegible]ility is that the severe damage of the sinus [illegible] has led to sinus arrest with cardiac stand[illegible] [illegible]n most cases of sinus node damage, atrial [illegible]tion or occurrence of a substituting pace[illegible] prevents a fatal outcome of ceased impulse [illegible]tion Nevertheless, Adams-Stokes attacks [illegible]en fatal cardiac standstill are well known [illegible]ications of severe sinus node lesions. In [illegible]ck of conclusive evidence from ECG regis[illegible] in our case death from sinus arrest can [illegible] proved, and sudden death from ventricular [illegible]tion induced by sarcoid involvement of the [illegible]rdium can not be excluded.

[illegible] interruption of the left bundle branch of [illegible] conducting system in our patient may [illegible]ve caused a left bundle branch block, but [illegible]rdly directly related to her death. Sudden [illegible] as seen in our patient has been reported in [illegible]han half of the cases with myocardial [illegible]osis. Roberts and associates have also [illegible] that sudden death may be the initial [illegible]tation of undiagnosed sarcoidosis.

[illegible]ase No. (Table I) died fr m coronary [illegible]sease. Sarcoidosis was an incidental find[illegible] [illegible]utopsy The small subendocardial granulomas found in the interventricular septum near the bundle of His and in the right atrium adjacent to the sinus node were probably not of any clinical significance in this case.

Disturbances of cardiac rhythm are the most common presenting clinical symptoms of cardiac sarcoidosis, as first described by Salvesen. The arrhythmias and the conducting disorders may be transient, but in most patients they are permanent.[3] Ventricular tachycardia and complete AV block are among the arrhythmias most frequently reported.[illegible] Other intraventricular conduction disturbances do also occur. Atrial arrhythmias are less frequently seen, but occasional cases of atrial fibrillation, atrial flutter and atrial ectopic rhythm have been described.[illegible]

It appears, therefore, that both apparently innocent and more serious cardiac arrhythmias may indicate cardiac involvement in patients with sarcoidosis. As such involvement may have serious prognostic and therapeutic implications, patients with sarcoidosis should be observed regularly in order to detect cardiac arrhythmias. Some cases of sudden death, so often seen in these patients, might thereby be prevented.

Summary

In a consecutive series of 2,950 routine autopsies two of 13 cases with sarcoidosis had cardiac involvement, one of which showed extensive granulomatous lesions in the sinus node. It is suggested that sudden death in this 52 year-old woman was caused by cardiac sarcoid involvement, possibly by leading to sinus arrest with cardiac standstill. However because of the lack of electrocardiographic evidence sudden death from ventricular fibrillation can not be excluded. As sudden death is a well-known complication of sarcoidosis, all such patients should be regularly screened for cardiac involvement in order to prevent fatal arrhythmias.

I am deeply grateful to Per F Marton, M D, for [illegible] assistance in preparing this manuscript.

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Hereditary bundle branch system defect
A new genetic entity?

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Cardiac conduction disorders sometimes appear as the expression of an autosomal dominant trait. A unique example was that of a large family descending from a probably affected ancestor who transmitted the trait to his descendants with 2 of his 3 wives. In this kindred there were major well-defined conduction disorders, such as complete heart block, right bundle branch block, bifascicular block, left anterior hemiblock, and minor someones equivocal, abnormalities of the conducting system such as mild degrees of left axis deviation and an r′ configuration of the QRS in right precordial leads. Only major disorders were reported.

Recently we surveyed a second kindred where several cases of heart block were observed between 1941 and 1958. This survey led to a third kindred presenting predominantly mild forms of the trait.

In the present paper our aim is to (1) give an account of the three kindreds, including minor conduction abnormalities as well as major ones, (2) suggest a hereditary defect of the bundle branch system with its manifest expressions and *formes frustes* and (3) compare the three series together and with other series from the literature, and discuss heterogeneity in the group of hereditary block.

Materials and method

The three kindreds were separate rural autochthonous families, each descending from a common ancestor and coming from three separate parts of Lebanon. They were surveyed because they showed cases of familial block. The survey included a clinical and electrocardiographic examination, and, in most affected cases, fluoroscopy or radiography of the chest. All data were collected and interpreted by the same observer.

Criteria. Criteria for diagnosis of bundle branch block and hemiblock were mainly those of the New York Heart Association[11] and of Rosenbaum, respectively with some small personal modifications. In infants with morphologic features of right bundle branch block (RBBB) we accepted QRS duration of 0.08 to 0.10 sec., instead of 0.10 to 0.12 sec., and we mainly relied on right ventricular activation time (RVAT) to recognize complete from incomplete RBBB. An RVAT of 0.05 to 0.06 sec. was required for the diagnosis of incomplete RBBB, 0.08 sec., at least, for complete RBBB. These values of RVAT were also found useful in doubtful adult cases to distinguish complete from incomplete RBBB.

Left axis deviation required for diagnosis of left anterior hemiblock was at least ± 0 degrees in babies and toddlers, −10 degrees in older children, −20 degrees in adolescents, and −30 degrees in adults. In the adult with horizontal heart and clockwise rotation we required an axis of at least −45 degrees.

Right axis deviation required for diagnosis of left posterior hemiblock was at least +150 degrees in babies, +130 degrees in older children and +120 degrees in adolescents and adults.

In left or right axis deviation associated with RBBB the axis was that of the 0.04 to 0.05 sec. initial portion of the QRS.

An r′ pattern (Figs. 4 and 5) was frequently encountered in the right precordial leads, and consisted of an rr′s or rsr′s configuration of the

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Table I Analysis of conduction anomalies encountered in the three families reported

	Family "Z"						Family "M"						Family "T"					
			Age						Age						Age			
	Sex		Average				Sex		Average				Sex		Average			
	M	F	M	F	Range	Total	M	F	M	F	Range	Total	M	F	M	F	Range	Total
Number	137	126				263	40	52				92	103	95				198
Number examined	125	117	16	17	0-78	242	30	41	20	21	0-65	71	99	93	23	20	0-80	192
Affected (A)	38	20	20	19	0.1-78	58	11	11	24	30	3-64	22	30	18	31	23	1-75	48
First degree relatives (B)	38	42	20	19	0-76	80	11	15	24	14	0-64	26	40	45	22	19	0-80	85
Ratio A/B	1	0.47				0.72	1	0.73				0.84	0.75	0.4				0.64
Type of anomaly																		
RBBB																		
Complete	13	5	18	15	0.7-80	18		1		11		1	1		2		2	1
Incomplete	8	1	21	6	1.5-38	9	1		12			1	9	1	23	12	2-45	10
With LAD	3	4	19	39	2-55	7							1		70			1
LAD alone																		
> −30°	1		72			1	3	3	28	54	20-58	6	4	1	53	60	6-69	5
< −30°	1	1	6	68	6-68	2	1	2	35	25	6-43	3	3	3	32	33	4-65	6
r′ pattern																		
Alone	9	7	18	15	5-34	16	4	2	9	30	3-30	6	8	10	19	18	4-35	18
With LAD	1	2	12	23	12-26	3							4	3	45	12	1-75	7
Complete heart block	2		56		40-75	2	2	3	22	48	18-63	5						

QRS, or an embryonic r′ within the S wave. The r′ was usually at, or under 2 mm. and *not terminal*, with a qr′ interval (beginning of r to summit to r′) of 0.05 to 0.06 sec., usually broad terminal forces in the frontal plane, and frequently prolonged QRS interval. The r′ wave of the common, normal rSr′ configuration is narrow usually terminal, and decreases or disappears in leads one intercostal space below V_{1R} and V_{1R}. The abnormal r′ persists or increases in these leads. At times, with taller r′ distinction with incomplete RBBB is not easy. The value of this *r′ pattern will* be discussed later.

Results

Conduction anomalies encountered in the three kindreds, with already published data, are presented in Table I.

Family "Z" (Fig. 1). This kindred from the South, already reported in part,[18] included 266 known living members descending from a polygamous progenitor with three wives. This man was a cardiac patient with a slow heart rate and syncopal attacks. He died suddenly in his sixtieth year. His parents were not blood related, and he was not blood-related to his wives.

Out of 242 descendants examined up to July 1978, 58 showed conduction anomalies including 27 cases with RBBB, three cases with left axis deviation (LAD) alone, seven cases with RBBB associated with LAD (not including the proband) (Fig. 6), 19 cases with r′ pattern (Fig. 5), and the two following cases of complete heart block (CHB).

1. The proband, Case A II 1,* 73 years old, showed RBBB with LAD, then intermittent CHB with syncopes, ventricular rate at 35, and QRS of the RBBB type. A pervenous pacemaker was successfully inserted.

2. His first half-brother from the second wife, 40 years old, was found to present in 1972 a CHB with ventricular rate at 36, and a QRS of the left bundle branch block type. He was still symptom free 6 years later.

Follow-up. Thirty two affected individuals and

*Capitals A, M, and T designate, respectively, branch A of Family "Z," and branches of Families "M" and "T."

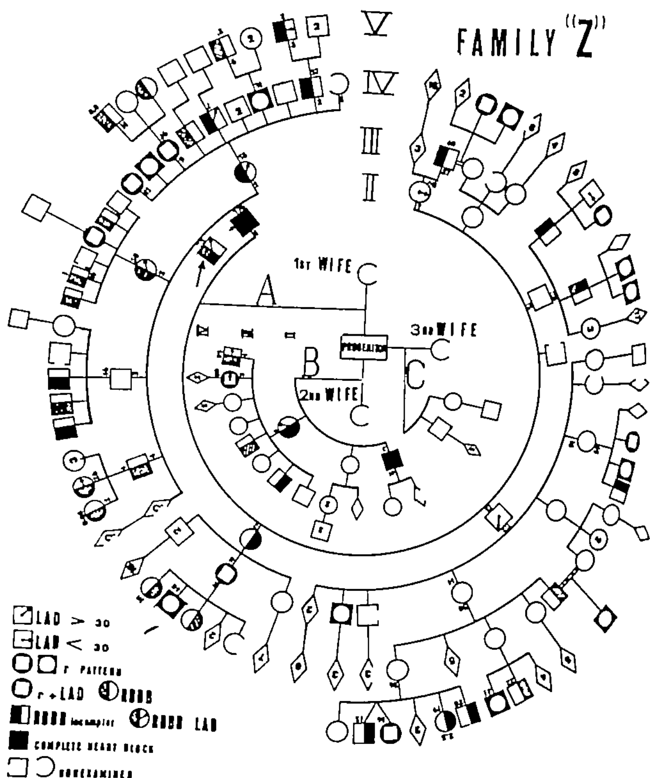


Fig 1 Pedigree of Famil "Z" Age is indicated abov symbols, serial number below Descendants of the three wives of the Progenitor are designated by C pitals A, B, nd C the Proband is designated by an arrow and t squares at the ages of 73 and 75 Abbrevia ions *RBBB* = right bundle branch block *LAD* = left axis deviation (Modified. From Stéphan, E H reditary bundle-branch system defect. Survey of family ith four affected generations, AM. HEART J 85 89 19 8)

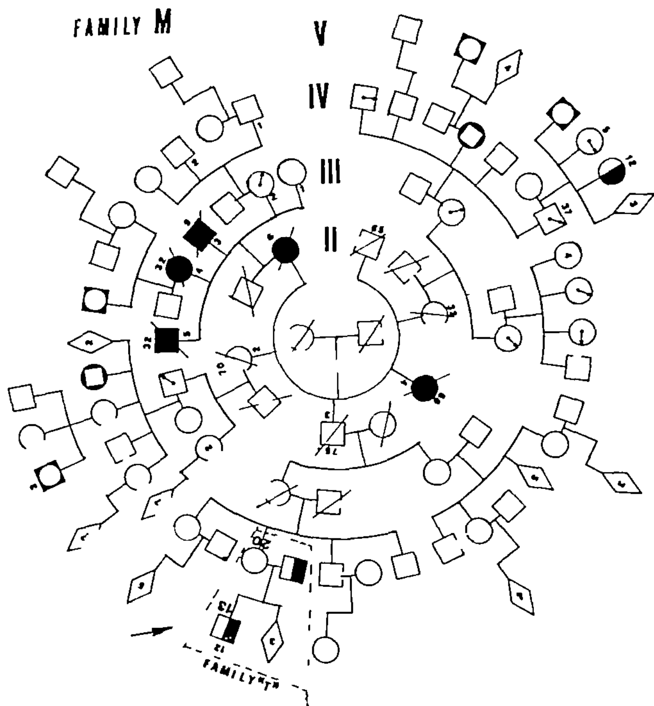


Fig. 2. Pedigree of Family "M." Arrow indicates family of boy M V 12, with his mother unaffected, and his father from Family "T" affected with incomplete RBBB. Note that mother's family branch is free from the trait.

almost all their first degree relatives were examined again, 3 years later in 1978, and no changes were seen in the ECGs.

Family M (Fig. 2) This kindred, from the North, was known since 1940. The two ancestors of the first generation were not blood related and died at an advanced age. Five cases of heart block, of which four were reported, occurred between 1940 and 1961, and none since then.

Female M II 1 (Fig. 7) 62 years old, presented syncopes with 2 degree heart and LAD; then, LAD alone for 2 years;

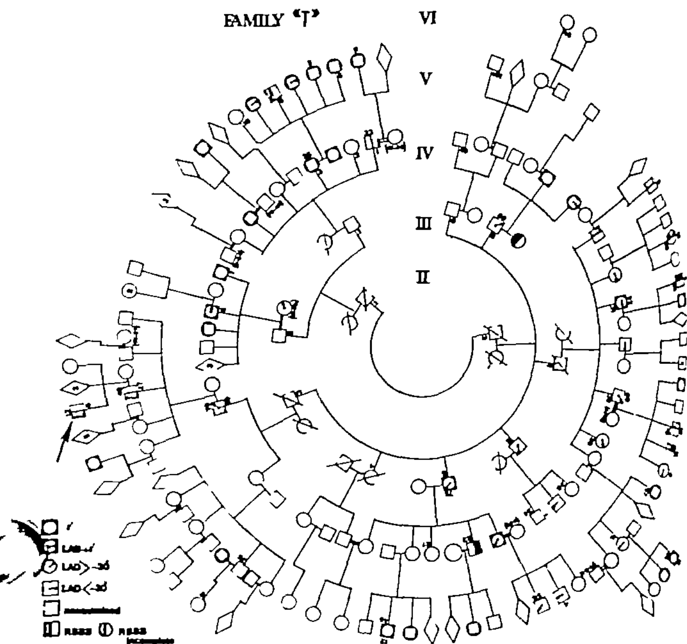


Fig 3 Pedigree of Family "T" Individual T VI-8, 13 years old, indicated by an arrow t the middle extreme left, is boy M V 13 from Family M in his paternal family with his father and grandfather all three affected with incomplete RBBB Grandfather also show LAD

with wide QRS, syncopes, and sudden death.

Her second sister a 60-year-old nun and her *third daughter* 32 years old, both asymptomatic showed 2 degree heart block with a prolonged P R interval and RBBB They died suddenly one month and 2 years later respectively

Her first son 19 years old presented with syncopes with CHB a ventricular rate at 28 wide QRS, and died suddenly 2 years later

Her second son, 20 years old presented with missed heart and pulse beats on physical examination, and 2 years later a slow heart rate. Sn ECGs (Fig. 8) during the following 10 ye showed a progressive slow course from a 2:1 he block to CHB Sudden death after repe attacks of ventricular tachycardia occurred at t age of 32 years.

All five cases had a normal regular pulse a heart rate prior to 2 degree and 3 degree he block

Female M II 1 and her husband had a f remote common ancestor Two ECGs of t

husband in 1954 and 1958 were noted as being normal.

The kindred was surveyed in 1978, and 67 individuals were examined, of whom five were examined in 1956 and were noted to be normal. Four of these five individuals were still normal, while the fifth one, Female M III 2, now aged 58 years, showed a LAD at −40 degrees in a semihorizontal heart. The survey disclosed 17 individuals with conduction disorders, and included one case of complete RBBB in a 12-year-old girl, nine cases with LAD six cases with r′ pattern, and one case with incomplete RBBB (Male M V 13)

Incomplete RBBB in *M* V 13 was unexpected since his maternal family branch was free from the trait. We soon found that his father coming from another family Family "T" was affected with incomplete RBBB and his paternal grandfather too (*Fig. 9*). *This led to a survey of the* father's Family "T

Family "T" (Fig 3) This family came from the North, with no blood relationship with Families "Z" and M. We examined 192 individuals out of 196 known to be alive in 1978. Forty-eight showed conduction anomalies, and included one cases of complete RBBB in a 2 year-old boy 10 cases of incomplete RBBB, one case of incomplete RBBB with LAD 11 cases with LAD alone, 18 cases with r′ pattern, and seven cases of r′ pattern associated with LAD

A fourth affected Family "F"? Several intermarriages occurred in the village between Family "T" and a certain Family "F probably affected, since it included the wife of T III-8, with RBBB, and the husband of T IV-3, with r′ pattern, and two other young individuals with LAD in a group of 10 persons who came to be investigated. This fourth family "F" could not be surveyed due to renewal of the war

Miscellaneous

ECGs of partners of married individuals were non relevant, except in a few instances in Families "M" and "T" represented in the pedigrees.

There was no sinus bradycardia, no prolonged P R interval, alone, no prolonged Q-T interval, and no dysrhythmias. Several individuals showed right axis deviation of the QRS, but were well below the normal upper limits for age.

Physical and chest radiological examination was non-relevant, and beside many cases of otospongiosis in Family "T" and adult diabetes in

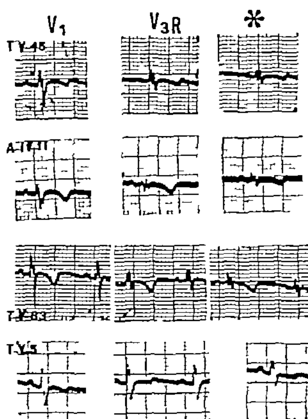


Fig. 4. Four examples of r′ pattern in right precordial leads. Lead indicated by an asterisk is recorded one intercostal space below V_{3R}. Note that the r′ wave is not terminal, and persists or increases in this new lead.

Families "Z and "M," there was no evidence of other cardiac or familial disease. A few cases in each family showed mild evidence of left ventricular hypertrophy to which no etiology could be clinically attributed.

There had been 43 stillbirths in Family Z," four in "M, and 12 in family "T Sudden death was noted five times in Z" and 11 times in "T" mainly in infants, and 7 in Family M" of which 5 were adults.

Echocardiograms and routine blood karyotyping in two individuals with RBBB and two with bifascicular block from Family "Z" were normal.

Comment

Inheritance. The trait is autosomal dominant with varying expressivity and penetrance, and many skipped generations, at times two, as in Family Z. In Family "M, a new trait was likely introduced by the mating of normal Female

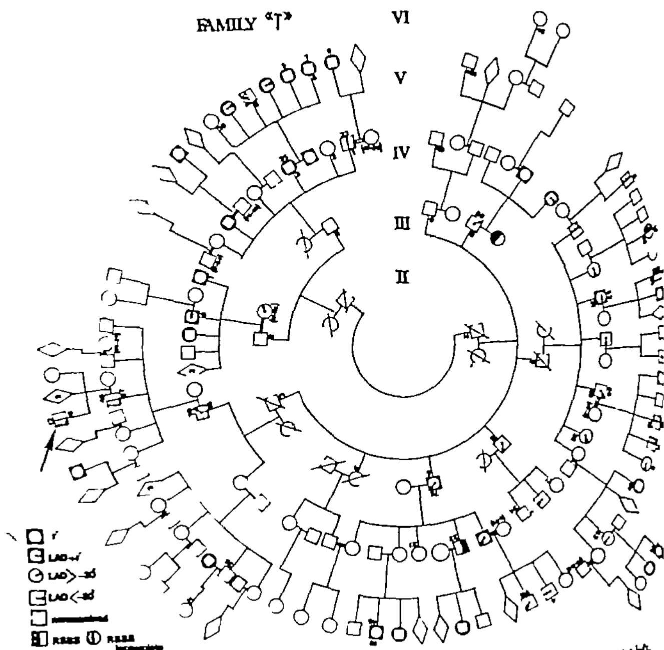


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Female M II 1 and her husband had remote common ancestor Two ECGs

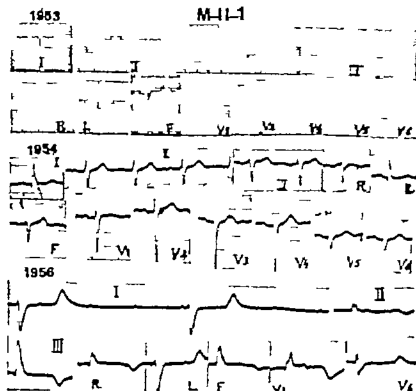


Fig. 7 Female M-II 1, from Family "M" 63 years old, showing: in 1953, 2:1 heart block with LAD; in 1954, LAD, alone; in 1956, complete heart block. (From Stéphan, E.: Bloc auriculoventriculaire familial, Arch. Mal. Coeur 64:333, 1961)

Onset. It is likely congenital, since age distribution, averages, and ranges are almost the same for affected and first degree relatives (Fig. 1, Table I). This also applies to bifascicular block, and not to complete heart block. Complete heart block has been of late occurrence in six out seven cases.

The defect. Originally impaired structures are within the bundle branch system, at the right branch and the anterior division of the left. Integrity of the posterior division, as attested by the absence of marked right axis deviation, is a remarkable feature and may indicate a defect below the root(s) of the posterior division, at the end of the His bundle or below.

Phenotypic expressions included RBBB, complete and incomplete, left anterior hemiblock, RBBB associated with left anterior hemiblock, and, possibly r′ pattern. Complete heart block may be a delayed developmental expression, or the effect of extraneous agent(s) such as focal ischemia, on a congenitally impaired conduction pathway.

The r′ pattern is not unlike that seen in atrial septal defect of the ostium secundum type. In one case, it has alternated with complete RBBB, mainly on deep inspirations and ensuing slow heart rate. In two cases from a small unpublished series it has preceded for many years complete RBBB. It was frequently associated with LAD. Common accompanying features, such as prolonged QRS duration, qr′ interval at 0.05 to 0.06 sec., and broad terminal forces in the frontal plane are suggestive of a right ventricular conduction delay possibly related to some minor partial form of RBBB. Alone, or with LAD it may represent a *forme fruste* of the genetic defect. However cases with r′ pattern are seen sporadically in unaffected family branches, and in many persons with apparently no hereditary defect. It is then of limited value as a genetic index, and necessitates further investigation.

Complete heart block seems to be of the low intraventricular type, since ventricular rate is slow and the QRS broad. Only one case is of unknown onset, the six others being in sinus rhythm before complete heart block. Precursors,

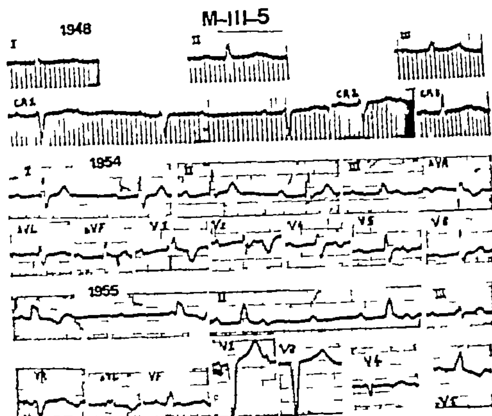


Fig. 8. Male M-III second son of Female M-II 1, showing: in 1948, a 2:1 heart block with questionable P R prolongation, normal QRS duration; in 1954, a 2:1 heart block, with prolonged P R, and RBBB, in 1955, complete heart block. (Modified, From Stéphan, E.. Bloc auriculoventriculaire familial, Arch. Mal. Coeur 54:333, 1961)

as documented in five cases, are RBBB with LAD LAD with ? degree heart block, 2 degree heart block with prolonged P R interval and RBBB. This looks to be a development from ... bundle branch block in a way not unlike Lenegre's disease Reasons for this development in only a few cases and its massive occurrence in only two generations of Family M" are unknown.

Comparison. Clinically structures initially involved are the same in the three series the right branch and anterior division of the left Differences are mainly quantitative according to the predominant impaired fascicle(s)

Family "Z right branch, alone, or with anterior division of the left

Family M" anterior division of the left branch.

Family "T" equally both, with predominance of mild forms.

This most likely indicates familial clinical types, but could not suggest heterog... of the three series.

Heterogeneity seems to exist in the group of hereditary block.

Our series looks to be of the low intraventricular type. In the literature available, ... series ... appear to be similar to ours.

The series of Waxman and associates is probably different and includes, exclusively ... cases of heart block, and no case of bundle branch or fascicular block It seems to be of the ... suprаHisian type, as indicated pathologically and by a His bundle recording.

The large series of Lynch and colleagues shows, exclusively first, 2 degree and 3 degree heart block, with normal QRS duration, and His bundle recording of the supraHisian type.

Epidemiological data to demonstrate heterogeneity are, however lacking.

Summary

A familial survey demonstrated mendelian inheritance in three large kindreds with conduction abnormalities and heart block. The transmission ... autosomal dominant, with varying expression

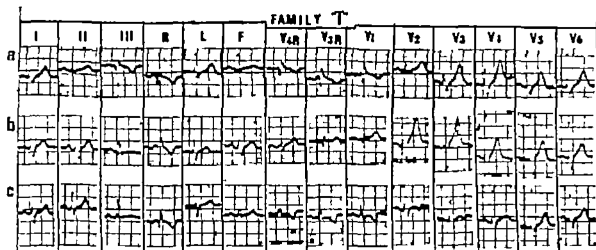


Fig. 9 Family "T" Three successive generations with incomplete RBBB· a, the grandfather T IV 15, 70 years old, also showing LAD· b, his fourth son, T V 27 40 years old; c, his grandson, T VI-8, 12 years old, who also is boy M-V 13 from Family "M"

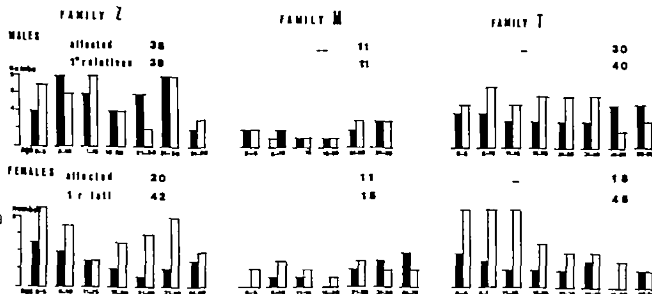


Fig. 10. Sex and age distribution of affected individuals and first degree relatives in the three families. The ratio affected to first-degree relatives is almost the same in the different age groups, which indicates congenital onset.

and penetrance, apparent male preponderance, and congenital onset.

Manifestations included right bundle branch block, left axis deviation, and right bundle branch block associated with left axis deviation. Complete heart block proved almost always to be a late event, and developed in all documented cases from bilateral bundle branch block. An r' pattern, most likely representing a right ventricular conduction delay is discussed.

Analysis indicated a defect originally impairing the bundle branch system, predominantly the right or the anterior division of the left.

Comparison with other series from the literature suggested heterogeneity in the group of hereditary block.

Addendum

A new case of RBBB associated with LAD at −90 degrees was found in an otherwise normal 48-

day-old baby boy second son to Male A IV 7 from Family "Z" (Fig. 6) To the best of our knowledge, this is the youngest case of congenital bifascicular block and, along with this ascendants, constitutes a unique lineage of bifascicular block through four successive generations.

We wish to thank Father J Lobstein, Professor of Biochemistry and Dr Josette Naffah, Professor of Genetics, Faculté de Médecine, Université Saint-Joseph, Beirut Miss Hoda Zurayk, Ph.D Associate Professor of Epidemiology and Biostatistics, American University of Beirut, Dr Chawki Hachem, a young dental surgeon who volunteered in part of this fieldwork and Dr Roland Sidawy for his expert photographic contribution which saved many documents from fire during the Lebanese War

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Limitations of the cardiokymograph for assessing left ventricular wall motion

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The detection and localization of abnormal left ventricular wall motion is important in the evaluation of patients with proven or suspected coronary artery disease. The analysis of left ventricular wall motion has been accomplished primarily by cineangiographic methods which require cardiac catheterization, thus limiting the number of studies that can be performed. Accordingly, a simple, sensitive, accurate, and reproducible noninvasive technique would be desirable for evaluating patients with suspected ischemic heart disease and for following patients with known wall motion abnormalities.

The cardiokymograph (CKG), formerly the displacement cardiograph, was first described by Vas. This new noninvasive instrument has been reported to be reliable for detecting left ventricular wall motion as compared to biplane cineangiography. One disturbing feature of the latter study was the recording of false abnormal wall motion patterns by CKG in some normal subjects. The device has been advocated for distinguishing between restrictive cardiomyopathy and constrictive pericarditis, for detecting coronary artery disease in patients with falsely negative treadmill exercise tests, and for identifying the falsely positive treadmill test. However, no reproducibility studies have been reported with the instrument. Therefore, we sought to evaluate the reliability and reproducibility of the CKG by comparing its results to those of simultaneous wall motion videotracking and by obtaining multiple CKG recordings in normal subjects, in patients with coronary artery disease, and in patients with mitral regurgitation.

The reliability of wall motion videotracking for assessing left ventricular wall motion has been demonstrated in several studies which have compared its results to those of cineangiography.[4-6] Videotracking the fluoroscopic cardiac silhouette is a relatively sensitive technique which has been used to detect serial changes in hypokinesis or dyskinesis during the course of acute myocardial infarction, with intravenous propranolol, and during isometric handgrip exercise. Furthermore, while studying the effects of orally administered pharmacologic agents on regional myocardial contraction, we have demonstrated the reproducibility of carefully performed videotracking studies.[11-]

Methods

Patient population. The study population was composed of four groups. Group 1 consisted of 27 patients who were studied from one week to 33 months (average 17 months) after a transmural myocardial infarction. There were 22 males and five females who ranged in age from 34 to 76 years. Each patient underwent simultaneous CKG and wall motion videotracking. Group 2 consisted of 21 normal subjects in whom CKGs were recorded. There were 18 males and three females who ranged in age from 19 to 35 years. In five of the normal subjects, CKGs were performed

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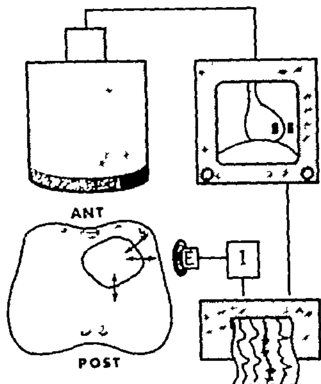


Fig. 1 Diagram of the equipment positions relative to a cross-section of the thorax for the videotracking, cardiokymography comparison study. *The arrows represent cardiac wall motion in the three directions analyzed by the two devices.* Note that the cardiokymograph is oriented perpendicular to the direction of the motion being studied and the image intensifier is oriented parallel to the direction of motion. Therefore, the tracking cursors follow the silhouette of the area of the left ventricular wall that is moving perpendicular to the center of the cardiokymograph coil (see text). *ANT* = anterior chest wall, *POST* = posterior chest wall. *E* = external oscillator; *I* = internal oscillator.

on two occasions, one to seven days apart, under identical conditions. Group 3 consisted of nine men with stable angina pectoris who had CKGs recorded on two separate days, less than a week apart and under identical conditions. Group 4 consisted of seven patients with marked mitral regurgitation (grades 3+ or 4+ on a scale of 4) documented by left ventricular cineangiography.

Cardiokymography. The CKG is a noninvasive instrument that records tissue movement in an electromagnetic field. A 10 cm. energized planar coil is held 5 to 15 mm. above the chest wall by a Plexiglas frame. Motion beneath the coil distorts an induced electromagnetic field which in turn alters the frequency of an external oscillator. This frequency is then compared to that of a manually operated internal oscillator in the attached control box and the difference in frequency is converted to an output voltage and recorded. The frequency response is flat from 0.1 to 75 Hz.

Wall motion videotracking. A commercially available device (Biotronics Heart Motion Videotracker) was used to track the fluoroscopic cardiac silhouette which was displayed on a Philips Plumbicon television system with the use of a 23 cm. image intensifier. The analog videotracking signal and CKG tracing were recorded simultaneously on a Honeywell Visicorder Photographic System. Lead II of the electrocardiogram and a phonocardiogram from the left second intercostal space were also recorded for timing purposes.

Cardiokymograph–videotracking comparison study. In the 27 Group 1 patients, videotracking and CKG recordings of cardiac wall motion were performed simultaneously in three positions corresponding to the anterior, lateral, and posterior left ventricular surfaces. Fig. 1 illustrates how the instruments are positioned to simultaneously record lateral left ventricular wall motion with the fluoroscope in the anterior-posterior position and the CKG positioned laterally at the level of the cardiac apex. The tracking cursors of the videotracker were aligned with the cardiac silhouette that faced the center of the displacement cardiograph coil as visualized under fluoroscopy. Therefore, both devices were evaluating the exact same segment of the left ventricular wall. The angle between the two devices was maintained at 90 degrees while they were rotated to record movement of the anterior and posterior walls. All tracings were performed during held inspiration with the patient instructed to avoid a Valsalva maneuver.

Chest position studies. The normal subjects in Group 2 had CKGs performed with the coil placed over electrocardiogram positions V_{1-6}, and recordings were made both at end-expiration and at full inspiration. Also, recordings were made posteriorly with the rim of the Plexiglas frame at the midline and the coil to the left in interspaces T_{1-10}. These posterior recordings were obtained during held mid inspiration.

Reproducibility studies. In five normal subjects from Group 2, recordings (described above) were done on a subsequent day under similar conditions. The patients in Group 3 had CKG recordings performed over electrocardiogram positions $V_{3,4}$ and V during held inspiration. The

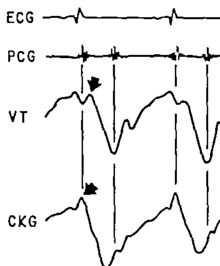


Fig. 2. Normal inward systolic left ventricular wall motion recorded simultaneously from the same site by both instruments. *The arrows* denote the early pre-ejection outward movement by both devices. Note that the motion pattern described by the videotracker *(VT)* lags behind that of the cardiokymograph *(CKG)* because of the inherent delay in the tracking circuit. Otherwise, the motion patterns are almost identical (see text). *ECG* = electrocardiogram, *PCG* = phonocardiogram.

recordings were then repeated one to seven days later under similar conditions.

Left atrial motion Patients in Group 4 had CKG recordings from the V_{4-6} position at end inspiration and posteriorly between T and T at held mid inspiration. Three of these patients underwent mitral valve replacement and subsequently had tracings performed in the early postoperative period prior to hospital discharge.

Analysis of wall motion Three patterns of abnormal wall motion were defined by both the CKG and videotracking tracings.

1. Normal pattern—After an early upward systolic pre-ejection movement there is a downward motion during ejection which represents the inward motion of the left ventricular wall[14] (Fig. 2).

2. Akinesis—After the early upward pre-ejection movement there is no further movement during systole.

3. Dyskinesis—Outward movement during systole that exceeds the pre-ejection movement (Fig. 3).

Results

Videotracking comparison In the 27 patients with previous myocardial infarction (Group 1)

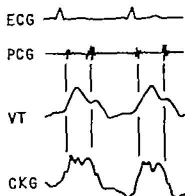


Fig. 3. Outward dyskinetic left ventricular wall motion recorded at the same site by both instruments.

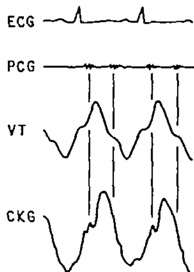


Fig. 4. Normal wall motion recorded by videotracking *(VT)* and late systolic outward motion recorded by cardiokymography *(CKG)* t the same posterior left ventricular site (see text).

there were 81 potential recording sites of which 77 sites could be recorded by one of the two techniques and 69 sites by both. Of the eight sites where technically adequate recordings could only be made with one of the instruments, six were unsuccessfully recorded by videotracking and two by CKG. Four of the six inadequate videotracking studies and both of the CKG failures were from the posterior left ventricular wall.

Identical wall motion was found in 52 of the 69 sites (75 per cent) adequately recorded by both instruments and 32 of these 52 concordant tracings exhibited abnormal wall motion. All 17 discordant sites demonstrated normal wall motion by videotracking and abnormal wall motion

Table IA. Frequency of wall motion patterns by cardiokymography at three anterior sites in 21 normal subjects

	V		V		V	
	EX	IN	EX	IN	EX	IN
Normal	50%	80%	35%	75%	10%	33%
Dyskinetic	36%	0	35%	10%	50%	33%
Akinetic	14%	20%	30%	15%	40%	34%

V correspond to the usual precordial electrocardiogram sites.
EX = expiration, IN = inspiration.

Table IB Frequency of wall motion patterns by cardiokymography at various posterior sites in 21 normal subjects

	T	T	T	T_{10}	T	T	AVG
Normal	48%	55%	42%	50%	45%	50%	[illegible]
Dyskinetic	27%	20%	20%	20%	20%	21%	[illegible]
Akinetic	25%	25%	38%	30%	32%	29%	[illegible]

T correspond to posterior intercostal spaces along vertical line through the electrocardiogram V position.
AVG = numerical average for the row

by CKG Twelve of these 17 sites were on the posterior wall and five were on the anterior or lateral wall. Fig. 4 is a representative example of posterior wall motion recorded from one of the 12 patients with discordant motion at this site and exhibits normal inward wall motion by videotracking and late systolic outward motion by CKG Left ventricular biplane cineangiograms performed within 60 days of the noninvasive study were available in five of these 12 patients and all showed normal posterior wall movement. Three patients had discordant anterior or lateral wall motion with normal wall motion by videotracking and abnormal movement by CKG All three patients had previous anterolateral myocardial infarctions. Also recent left ventricular biplane cineangiograms, which were available in o of the three demonstrated abnormal anterolateral wall motion

Studies in normal subjects In the 21 normal subjects (Group 2) there was a high incidence of akinesis or dyskinesis, which progressively increased from position V to V_6 when recordings were taken at the end of normal expiration. When recordings were taken during held inspiration, the incidence of abnormalities" was lower but still substantial, and the frequency increased from position V to V (see Table IA) Tracings during held inspiration were also made from the left posterior chest wall in the mid-scapular line (V at levels from the seventh to twelfth rib) These records also showed a high incidence of abnormal" recordings which seemed to be unaffected by the location of the recording (see Table IB)

Reproducibility studies In 14 individuals (five from Group 2 and nine from Group 3) tracings obtained on two separate occasions under identical conditions were examined for reproducibility The percentage of recording sites in all the subjects which were identical was 52 per cent and was not significantly different between the Group 2 subjects (50 per cent) and the Group 3 patients (55 per cent) The agreement between the two recordings in each subject was higher in the anterior sites (65 per cent) than in the posterior sites (38 per cent) Also anteriorly there was better correspondence between the tracings made during inspiration (75 per cent) than in the tracings obtained at expiration (48 per cent).

Cardiokymograms in patients with mitral regurgitation Seven patients with severe mitral regurgitation were examined (Group 4), and all showed akinetic or dyskinetic wall motion patterns posteriorly in the T_{10} area. Three of these patients were studied postoperatively after successful mitral valve replacement and the apparent wall motion abnormality had disappeared (Fig. 5)

Discussion

Implications of the results. The results of our study suggest that the posterior left ventricular wall is the most difficult structure to record by either technique. Also, our studies in normal subjects show that the reproducibility of CKG records from the posterior wall was low with a high incidence of false abnormal wall motion recorded over the posterior left ventricle. The studies in patients with mitral regurgitation imply that the false abnormal wall motion recorded over the posterior wall by CKG may represent normal left atrial expansion during systole. This is consistent with the ability to detect the left atrial systolic "v wave by wall motion videotracking when the barium filled esophagus is tracked posteriorly Fluoroscopic determination of the position of the CKG coil in relationship to the heart demonstrated that the

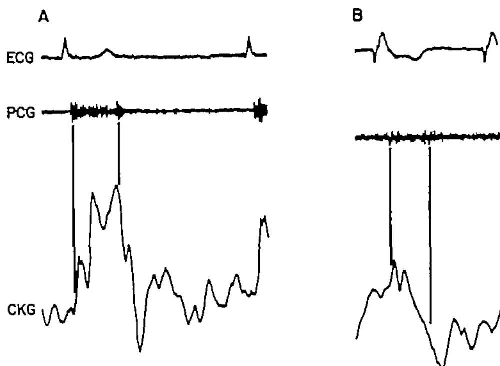


Fig. 5, A and B. *A*, Late systolic outward movement is recorded by cardiokymography *(CKG)* posteriorly at T in patient with marked mitral regurgitation. *B*, CKG recording at the same site in the same patient five days after successful mitral valve replacement and transvenous pacemaker insertion. Wall motion is now normal.

left ventricular apex was often quite anterior. Thus, the left atrium was the closest structure to the CKG coil no matter in what interspace the coil was placed on the back. An anterior apical position was especially marked in expiration; hence all our posterior wall recordings were done during held mid inspiration when the left ventricle was positioned more posteriorly. Unfortunately the characteristics of the CKG are such that it responds preferentially to the closest moving object because the amplitude of motion perceived by the instrument decreases exponentially with the distance between the moving object and the coil. For these reasons, the CKG used in this study was of limited value in the assessment of posterior left ventricular wall motion.

Both techniques readily recorded anterior and lateral left ventricular wall motion. The major problem in this area was the high incidence of false abnormal wall motion recorded by the CKG. This problem was also observed by Gay and associates, who found that one of six normal subjects exhibited anterior dyskinesis on the CKG recording. The characteristics of this instrument are such that it is most sensitive to the air gap surface closest to the coil.[14] Thus, if the chest wall is moving, this motion will dominate the recordings. In fact, the CKG has been used as an apex-cardiograph. However if the chest wall is immobile, then the heart lung interface will be the dominant movement recorded. In patients with prominent apical impulses, outward systolic movement will always be recorded over the apical area and this movement will extend for a variable distance around the apex depending on the heart size, the amplitude of this movement, and the forcefulness with which it displaces the chest wall. This apical phenomena can be reduced by recording during inspiration rather than expiration, so that the heart is separated from the chest wall and the thoracic apical impulse is lessened or obliterated. Also in a recent study by Diamond and co-workers,[15] a smaller coil was used over precordial areas away from the apex but determined to be over the heart by fluoroscopy and normal anterior wall motion was recorded by CKG in all 10 patients with normal motion by cineangiography.

Another feature of the CKG is that it responds best to one dimensional movement in an axis

perpendicular to the coil. Rotational movement can change the surface slope of the ventricle in relation to the coil and can be incorrectly interpreted as movement of the heart surface along the axis of the coil. Even when there is no chest wall movement, rotary movements of the apex may simulate akinesis or dyskinesis and obscure the normal contractile inward motion of this area. Indeed, our results demonstrate that false anterolateral wall motion abnormalities cannot be completely eliminated in all subjects even with inspiratory recordings. Therefore the CKG is of limited value for accurately detecting anterolateral wall motion abnormalities. By contrast, previous videotracking studies in normals have shown some hypokinesis over the apical area but no frank dyskinesis has been recorded.

Although the CKG is an inaccurate method for noninvasively predicting the quality of wall motion in a large part of the left ventricle, it could be valuable for the serial study of contraction abnormalities in patients with well-defined heart disease. However the results of our study suggest that the over-all reproducibility of this device in normal subjects and in patients with coronary artery disease is only fair at best. Despite efforts to return the subjects to the same position, to match the inspiratory efforts and to position the coil over the same anatomical landmarks, the recorded wall motion patterns often differ from day to day. The reasons for this deficiency were not elucidated in the present study. Recently a smaller probe has been tried in animal and in human studies utilizing fluoroscopy to position the coil over the cardiac area of interest. Perhaps these and other modifications can improve the reproducibility of the technique, but this remains to be demonstrated.

Advantages and disadvantages of the cardiokymograph. The CKG has several advantages. First, it is a low-cost instrument both in terms of initial purchase price and maintenance. Second, it is easy to operate and requires little training to use properly. Third, it is extremely sensitive to any motion and therefore, potentially could detect a smaller area of abnormal wall motion than could be detected by other techniques. Finally there is no known toxic effect of an electromagnetic field of this magnitude being placed through the body. On the other hand there are several disadvantages to the CKG. First, the wall motion detected and recorded cannot be quantitated.[1] This is mainly because the distance from the probe to the heart is unknown in most situations. Second, the technique is most accurate for recording the anterior left ventricular wall. Recordings near the apex often exhibit false wall motion abnormalities because of rotatory cardiac movement and chest wall movement in this location. Tracings from the posterior wall area may show late outward movement because of interference by the left atrium. Third, one cannot be certain exactly which structures are being recorded by the CKG because of the inability to visualize the underlying cardiac structures. Last, and probably most important, is the poor reproducibility with this technique.

Clinical applications. What initially seemed to be an attractive new device for noninvasively assessing left ventricular wall motion, now appears to have several limitations. Although the CKG has interesting applications in open-chest animal work, where it is useful to record wall motion without touching the heart, the exact use in closed-chest animals and humans remains to be demonstrated. Perhaps technical improvements in the future will establish its position in our noninvasive armamentarium.

Summary

In order to evaluate the reliability and reproducibility of the CKG we studied four groups of patients. In 27 patients with a prior myocardial infarction the CKG recordings were compared to simultaneous wall motion videotracking. Identical wall motion was recorded in 76 per cent of left ventricular sites and most of the discordant sites were false abnormal posterior wall motion recorded by the CKG. The second group consisted of 2[illegible] normal subjects studied by CKG only and 33 per cent displayed anterior dyskinesis during expiration. The third group consisted of nine stable patients who were studied on two separate days by CKG and identical wall motion was recorded in only 55 per cent of the sites on the two recordings. The final group consisted of seven patients with mitral regurgitation and all had late systolic outward movement posteriorly. Systolic wall motion was normal postoperatively in the three patients who underwent valve replacement. We conclude that: (1) the usefulness of the CKG is limited by the frequent recording of false wall motion abnormalities in normal subjects, (2) that anterior wall motion abnormalities can be

reduced by recording during inspiration, (3) false posterior wall motion abnormalities may be due to systolic left atrial expansion, and (4) cardiokymography recordings are often not reproducible.

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Prognostic value of echocardiographic evaluation of septal function in acute anteroseptal myocardial infarction

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The echocardiogram is a sensitive technique for evaluating the contraction of individual segments of left ventricular myocardium. Although a high incidence of echocardiographic septal abnormalities have been demonstrated in patients with acute anterior myocardial infarction,[1-11] it is unclear whether these abnormalities have any clinical significance. Therefore, we undertook a prospective study of patients with acute transmural anteroseptal myocardial infarction to determine (1) whether the electrocardiographic evidence of septal infarction correlated with abnormalities of the portion of septum seen on M mode echocardiograms and (2) whether the echocardiographic evaluation of the septum had a useful role in predicting clinical course and prognosis.

Methods

Patient population Between November 1976, and August, 1977 standard M mode echocardiography was performed within 24 hours of admission on all patients admitted to The Mount Sinai Hospital with a diagnosis of acute anteroseptal myocardial infarction. All patients included in this study had a characteristic history of chest pain, an electrocardiogram which evolved abnormal Q waves in the anterior leads (Lead V as a minimum) and enzymes diagnostic of myocardial infarction. None of our patients had a previous anterior wall myocardial infarction, previous cardiac surgery pre-existing left bundle branch block, or any evidence for right ventricular diastolic volume overload or cardiomyopathy Patients were classified clinically by the Killip classification.

Echocardiograms. All echocardiograms were obtained at the bedside in the coronary care unit with a Unirad or Irex echocardiograph utilizing a 2.25 MHz, 7.5 or 10 cm. focused transducer and recorded on a strip-chart recorder A continuous M mode sweep from the aortic root to the posterior papillary muscle of the left ventricle was performed from an interspace where the mitral valve could be visualized with the transducer perpendicular to the chest.

Echocardiographic measurements. Septal motion and systolic thickening were measured in the standard position at the level of, or just below, the posterior leaflet of the mitral valve. Septal motion was taken as the excursion of the left side of the septum from end-diastole, taken at the peak of R wave, to its maximal systolic excursion. Septal excursion greater than 3 mm. was considered normal. Septal thickness was measured at mid-diastole, before the onset of the P wave, and at the point of maximal systolic thickening. Septal thickening was expressed as the change in thickness as a percentage of the mid-diastolic

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Table I Clinical, electrocardiographic and echocardiographic findings

		IVS			*LVPW*		*LV diastolic dimension (cm.)*	*PR-AC (seconds)*	*Q waves*	*Class*	*BBB*
Patient	*S/A*	*Thickness (mm.)*	*% Thickening*	*Excursion (mm.)*	*Thickness (mm.)*	*Excursion (mm.)*					
L. U	M/71	11	0	3	12	12	5.4	0	V_{1-4}	IV†	–
R. B.	M/53	13	0	Paradox	11	22	5.9	0.12	V	III	RBBB
F. G.	M/63	9	10	0	8	12	4.6	0.10	V_{1-4}	II	–
H. L.	M/73	10	0	3	8	7	5.7	NA	V	III	RBBB
J. N.	M/66	12	0	0	9	11	5.2	0.14	V	II	RBBB
A. D	M/60	12	36	8	10	14	4.8	0.06	V_{1-4}	I	–
R. A.	M/46	10	20	6	9	16	4.2	0.12	V_{1-4}	I	–
M. N.	M/77	8	50	8	7	16	5.3	0.10	V_{1-4}	I	–
D. H.	F/49	9	100	11	10	17	4.8	0.10	V	I	–
B. G.	M/78	11	78	7	11	16	3.8	NA	V_{1-4}	I	–
R. B.	M/59	9	33	7	9	12	4.3	0.08	V_{1-4}	I	–
E. W	F/79	12	30	7	11	10	5.0	NA	V	II	–
P. M.	F/74	8	25	6.5	10	9	5.0	0.08	V	I	–
E. W	M/68	12	50	12	9	10	6.6	NA	V	I	–
M. T	F/66	11	11	0	10	13	5.0	0.01	V	IV†	–
R. T	M/63	8	0	0	9	11	6.4	0.10	V	III	RBBB LAH
A. C.	F/71	10	0	Paradox	10	10	4.4	NA	V	III	LBBB
B. M.	M/72	11	8	Paradox	11	12	3.8	0.10	V_{1-3}	I	–
A. M.	M/69	13	0	5	11	17	6.0	0.05	V	IV†	–
M. V	M/56	10	0	3	8	6	7.3	0	V	IV†	RBBB
R. B.	M/60	11	0	7	14	14	4.9	0.08	V_{1-4}	I	–
B. B.	M/60	10	0	Paradox	10	12	4.1	0.09	V_{1-4}	II	–
R. M.	F/86	11	33	4	12	15	4.8	0.10	V	II	–
D. K.	F/64	5	40	8	8	9	4/8	NA	V	II	–
M. S.	M/63	12	25	8	12	12	5.4	0.09	V_{1-4}	I	–
F. L.	M/68	9	0	Paradox	9	10	3.9	0.04	V_{1-2}	III	–
M. M.	F/74	14	29	3	11	9	3.6	0.05	V	II	RBBB
F. A.	M/63	10	0	0	8	9	6.0	NA	V	IV†	–
M. A.	F/68	8	50	8	9	11	5.6	NA	V_{1-4}	I	–
R. A.	M/70	11	63	12	10	12	5.0	0.10	V_{1-4}	I	–
M. S	M/83	8	−14	Paradox	10	11	4.8	0.10	V	IV†	–
E. R	F/80	12	25	4	9	12	4.2	NA	V_{1-6}	II	–
B. S.	M/50	10	20	5	10	14	5.0	0.12	V_{1-4}	I	–
R. R.	M/71	10	40	5.5	9	13	4.8	0.10	V	I	–
A. W	M/66	11	0	Paradox	11	12	4.0	0.02	V_{1-4}	III	–
A. G	M/62	13	25	6	11	18	5.5	0.10	V	I	–
N. S.	M/56	12	−9	Paradox	12	14	4.2	NA	V_{1-4}	III	–
N. P	M/51	10	28	6	10	10	3.8	0.06	V	I	–
F. L.	M/63	10	44	11	9	8	4.5	0.10	V_{1-4}	I	–
R. M.	F/84	10	−22	Paradox	10	12	4.2	0.04	V	II	–

† = patient died.
also old inferior wall MI
Abbreviations: S/A = sex/age, IVS = interventricular septum; LVPW = left ventricular posterior wall, BBB = bundle branch block; NA = not obtainable.

thickness. The normal value for septal thickening in our laboratory (range 20 to 60 per cent) was obtained from 20 age-matched normal individuals and is similar to that reported by others.[13] Septal function was considered normal if both excursion and systolic thickening were normal. Abnormal septal function denoted abnormal excursion and/or systolic thickening. Left ventricular posterior wall motion, left ventricular diastolic size, and the PR minus AC interval were also examined. All echocardiograms were interpreted without knowledge of the clinical data. Statistical analysis was performed by the Chi-square method with Yates correction for continuity

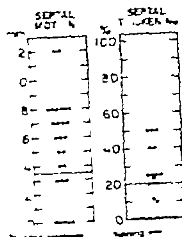


Fig. 1. Septal motion and systolic septal thickening in 40 patients with anteroseptal myocardial infarction. Each dot represents the findings in one patient.

Results

Sixty three patients met the criteria for entry into the study. Two patients died before echocardiograms could be obtained. Of the remaining 61, echocardiograms suitable for interpretation were obtained on 40 patients. Of these, 29 were men and 11 were women, with a mean age of 66 years (range 46 to 86 years). The clinical and echocardiographic findings are summarized in Table I.

Echocardiographic septal findings. The distribution of measurements of septal excursion and systolic thickening in our patients is seen in Fig. 1. Septal excursion was normal in 23 patients (58 per cent) and abnormal in 17 (42 per cent). Septal thickening was normal in 21 patients (52 per cent) and abnormal in 19 (48 per cent); three of whom exhibited septal systolic thinning. Twenty-one patients with both normal septal excursion and thickening were classified as having normal septal function. Seventeen patients with abnormalities of both excursion and thickening and two patients with abnormal thickening but normal excursion comprised the 19 patients with abnormal septal function. Representative echocardiograms of patients with normal and abnormal septal function are seen in Figs. 2 and 3, respectively.

Correlation between echocardiogram and electrocardiogram. Electrocardiographic evidence of septal infarction did not correlate with echocardiographic septal function. No difference in the distribution of abnormal Q waves in the precordial leads could be demonstrated between the patients with normal and those with abnormal septal function (Fig. 4).

Correlation between echocardiogram and clinical course. Of 21 patients with normal septal function, five (24 per cent) demonstrated congestive heart failure in the first 24 hours after admission. All five patients with normal septal function and congestive heart failure were in Killip class II. Of the 19 patients with abnormal septal function, 17 (89 per cent) demonstrated congestive heart failure. The 17 patients with abnormal septal function and congestive heart failure included four in Killip class II, seven in class III, and six in class IV (Fig. 5). No patient with normal septal function died in the hospital while six patients with abnormal septal function died of pump failure in the hospital. Furthermore, no patient with normal septal function developed bundle branch block, whereas seven patients with abnormal septal function manifested a new bundle branch block. Septal function correlated with development of heart failure ($p < .001$), the development of bundle branch block ($p < .01$), and inhospital mortality ($p < .001$).

Other echocardiographic measurements. Eight patients had increased left ventricular end-diastolic dimension (> 5.5 cm.). Two of these were in Killip class I, three were in class III, and three were in class IV. Eight of 30 patients had a shortened PR minus AC interval, two were in class II, two were in class III, and four were in class IV. In ten patients, this measurement could not be obtained. In two patients, both left ventricular end-diastolic dimension and PR minus AC interval were abnormal, both patients were in class IV and died.

Discussion

The most important finding in this study is the favorable short term prognosis associated with an echocardiographically normal septum in patients with acute anteroseptal transmural myocardial infarction. Of patients with normal septal function, 24 per cent developed congestive heart failure, none developed a complete bundle branch block, and none died in the hospital. Of the patients with abnormal septal function, 89 per cent developed congestive heart failure, 37 per cent developed a complete bundle branch block, and 31 per cent died in the hospital.

Similar findings regarding prognostic impor-

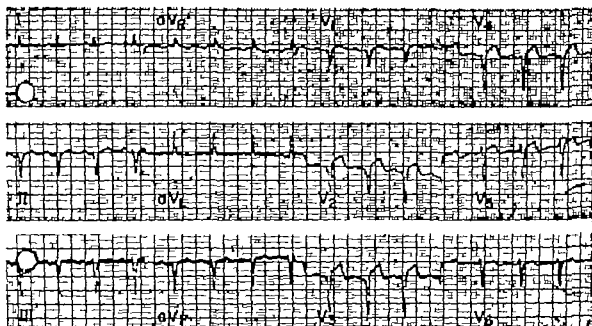


Fig. 2A. Representative electrocardiogram of a patient with an acute anteroseptal myocardial infarction and normal septal motion and systolic thickening.

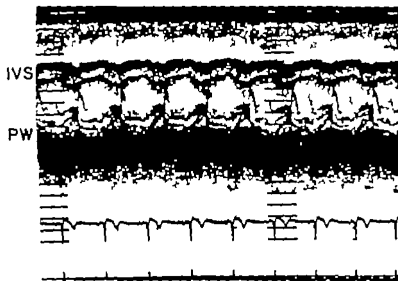


Fig. 2B. Representative echocardiogram of the same patient discussed in Fig. 2A. *IVS* = interventricular septum, *PW* = left ventricular posterior wall.

tance of septal function have also been reported in patients undergoing cardiac surgery for ventricular aneurysm. Dillon and co-workers reported septal excursion as evaluated in the standard position in 16 patients who underwent aneurysmectomy. Eight patients had normal excursion and all survived surgery. Of eight patients with abnormal excursion, five died.

We found a lower incidence (48 per cent) of septal abnormalities in our patients with acute anteroseptal myocardial infarction than the 85 per cent reported by Corya and colleagues [9-11] and the 100 per cent reported by Heikkila and colleagues. This difference in incidence of septal abnormalities may be due to difference in technique. We evaluated the septum in the standard

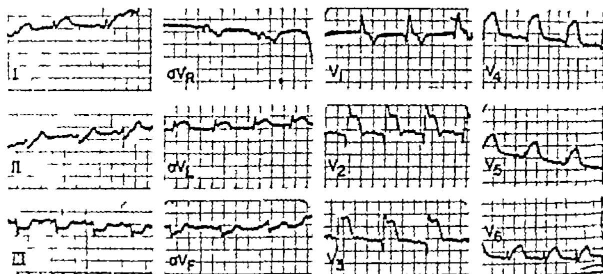


Fig. 3A. Representative electrocardiogram of a patient with an acute anteroseptal myocardial infarction complicated by bifascicular block.

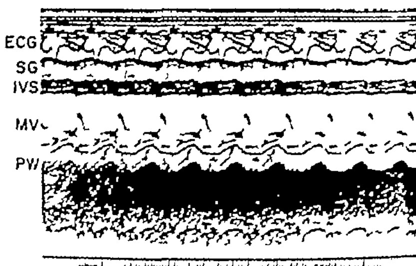


Fig. 3B. Representative echocardiogram of the same patient discussed in Fig. 3A. Note the absence of septal excursion and systolic thickening. SG = Swan-Ganz catheterization; MV = mitral valve.

position just below the mitral valve while Corya and associates and Heikkila and colleagues also utilized lateral scanning in multiple interspaces and epigastrium in an attempt to examine the entire anterior wall and septum. This more extensive scanning may increase the likelihood of finding abnormalities. While the evaluation of the septum in the standard position may be less sensitive in detecting abnormalities in patients with acute anteroseptal myocardial infarction, it appears to be more useful in predicting the patient's prognosis. As Corya [illegible] found abnormalities of the sept[illegible] per cent of their patients, this param[illegible] be used to distinguish among patients with different prognoses. They found that the combination of a large ventricle and abnormal mitral valve closure predicted a poor prognosis. Our data confirm that this combination is a poor prognostic sign, however it was found in only two of the six patients who died.

It should be noted that discrepancies also exist in patients with chronic anterior myocardial infarction. Corya and co-workers have reported abnormal septal motion in all their patients with chronic anterior myocardial infarction, while Gordon and co-workers found abnormal septal echoes in only one of seven patients with chronic

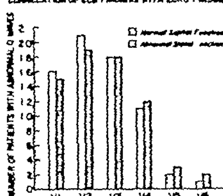


Fig. 4 Distribution of abnormal Q waves in precordial leads according to septal function. Note that all 40 patients had Q waves in Lead V

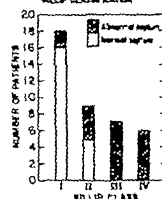


Fig. 5 Correlation of septal function and Killip classification.

anterior myocardial infarction. This difference may again represent variation in technique Gordon and colleagues examined the septum only in the standard position while Corya and associates also used lateral scanning. The findings of Gordon and colleagues are supported by recent work by Kolibash and colleagues,[15] who found that abnormal septal motion did not correlate with presence or absence of an electrocardiographic pattern of anteroseptal infarction, but did correlate with the presence or absence of isotopically determined septal perfusion.

The major limitation of our study is the fact that only 68 per cent of the patients had echocardiograms qualitatively acceptable. While this percentage is lower than the 92 per cent reported by Corya and colleagues, it is similar to that found by other investigators.[16] The included patients did not differ from the rejected patients in age, sex distribution, incidence of complications and mortality and presumably are a representative sample of the total group of patients. None of our patients had clinically significant mitral regurgitation which could have masked abnormal septal motion in patients with coronary artery disease.[17] Only one of our patients had complete left bundle branch block as the only other co-existing cause for abnormal septal motion besides coronary artery disease.[18]

We found no correlation between the electrocardiographic pattern of septal infarction and echocardiographically abnormal septal function as evaluated below the mitral valve. The reason may be that the echocardiogram visualizes the upper part of the septum, a portion not well represented on the surface electrocardiogram. Sodi-Pollares and associates[19] found that septal depolarization begins at mid-septum and that the high septum was electrically silent. Both the classic studies of Myers and colleagues[20] and the recent studies of Savage and co-workers[21] demonstrate that the high septum may be normal at autopsy in patients with anteroseptal myocardial infarction.

One possible explanation for the poorer prognosis in patients with acute anteroseptal myocardial infarction and echocardiographically abnormal septal function is that abnormalities of the portion of septum seen on the echocardiogram may indicate a large extent of septal involvement predisposing to pump failure and in some cases affecting the conduction system.

In conclusion, by examining the septum in the position below the mitral valve, we can obtain information about a portion of the septum not reflected in the standard electrocardiogram. Patients with acute anteroseptal myocardial infarction with abnormalities of this portion of the septum have higher morbidity and mortality rates than those with echocardiographically normal septal function.

Summary

To determine the clinical usefulness of echocardiography in patients with anteroseptal myocardial infarction, echocardiograms were performed within 24 hours of admission on 40 patients with acute transmural anteroseptal myocardial infarction. Twenty-one patients had normal septal motion and septal systolic thickening, and 19

patients had abnormalities of one or both of these measurements. Of the 21 patients who had normal septal motion and thickening, only five developed congestive heart failure, none developed bundle branch block, and none died. Of the 19 patients with abnormal septal motion and/or thickening, 17 developed congestive heart failure ($p < .001$), seven developed bundle branch block ($p < .001$) and six died ($p < .001$). Therefore, (1) electrocardiographic evidence of septal infarction does not correlate with abnormalities of the portion of septum seen on echocardiogram, and (2) patients with anteroseptal myocardial infarction and abnormalities of the septum on echocardiogram have more complications and a higher in-hospital mortality rate. These patients may have more extensive myocardial infarction predisposing to pump failure and possibly involving the conduction system.

We would like to thank Dr. Richard Gorlin for his review of this manuscript and Miss Fern S. Palmer for her secretarial assistance.

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Experimental and laboratory reports

Adverse hemodynamic and ultrastructural changes in dog hearts subjected to protein-calorie malnutrition

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There is a prevalent belief although not well documented, that the heart is spared of major untoward effects during prolonged periods of starvation. Although cardiac performance may be impaired during certain instances of chronic malnutrition, these have more frequently been associated with concomitant decreases in blood volume[1] or to specific vitamin deficiency states such as vitamin B, with resultant beri-beri heart disease, rather than to intrinsic defects in the integrity of myocardial structure and functional capacity

Protein-calorie malnutrition (PCM) frequently accompanies states of chronic congestive heart failure of various etiologies, primarily rheumatic, and may adversely contribute to the morbidity of chronic cardiac disease. This so-called cardiac cachexia as a clinical syndrome has been associated with increased morbidity and mortality following cardiac surgical interventions, although the immediate reasons for the poorer results following cardiac surgery have not yet been determined.

That protein-calorie malnutrition would adversely affect the structure and function of any viscus should come as no surprise and would be anticipated when a major portion of nitrogen and energy stores are depleted. An over-all decrease in heart weight in children who died of malnutrition has been described by Alleyne and co-workers, and may correlate with the decrease in heart size reported in fasting humans. In short term fasts, however the changes are more likely to be due to a decrease in plasma volume, total body sodium, and, hence, blood volume which would in turn affect ventricular filling.

The present studies were designed to determine whether or not sub-acute PCM would alter left ventricular (LV) contractility independent of these other variables previously identified as associated with prolonged periods of starvation.

Methods

A. Preparation of protein-calorie malnutrition model. Nineteen pure-bred beagle dogs, heart worm free, and averaging one year of age, were utilized for the experiments. Following a suitable period of observation at the Laboratory of Animal Medicine at the Cornell University Medical College to determine the absence of nutritional or other diseases, 11 of these animals were subjected to a hypocaloric, nitrogen-poor diet for an average of 50 days (range 36 to 65 days). The

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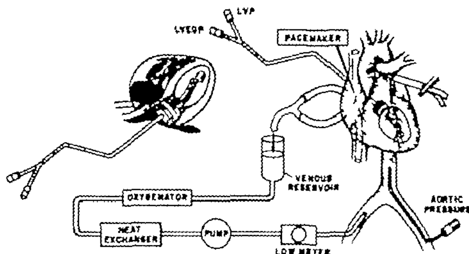


Fig. 1 Schematic representation of the preparation used to obtain isovolumetric LV contractions in control and protein-calorie malnutrition dogs.

where F is force (g – wt./cm², g – wt. = 980 dynes), P is instantaneous LV pressure, r is the internal (endocardial) ventricular radius (cm.), r is the external (epicardial) radius (cm.), and 1.36 is a conversion factor.

Since the ventricle was assumed to be spherical, r and r were solved from the equation

$$\text{Volume} = \tfrac{4}{3}\pi r^3$$

The internal ventricular radius was determined from the volume of the LV balloon and the LV muscle mass.[16] The specific gravity of the LV muscle was assumed to be 1.0[16-17] and the LV muscle volume was, therefore, determined by its weight.† Velocity of shortening of the contractile element (ce) was calculated from the equation

$$V_{ce} = \frac{dp/dt}{28P} X\ 2\pi r$$

where V_{ce} is velocity of contractile element shortening (cm./sec.), P is LV pressure (mm. Hg), and r is the midventricular radius (cm.). Force-velocity relations were determined by comparing the instantaneous relations between force and V_{ce} at 10 msec. intervals during the course of single isovolumetric beats. F was defined as the peak LV wall stress (force) when V_{ce} was zero. Because of the difficulties in extrapolating the force-velocity curves to zero tension, no attempt was made to estimate "V max."

Student's t test for unpaired data using an equal variance model was employed, assigning a one tailed significance level (p value) to each T ratio.

Hemodynamic studies. Following institution of cardiopulmonary bypass with stability obtained for at least 30 minutes, baseline hemodynamic measurements were obtained by progressively increasing the intraventricular (balloon) volume in stepwise increments from 3 to 21 ml. of saline. An intraventricular balloon volume of 9 ml. was selected as the intraventricular volume at which force-velocity relations were calculated.

Biochemical assays. Immediately following institution of cardiopulmonary bypass in all animals, full thickness biopsies of the anterior wall of the right ventricle were taken and were deep frozen immediately in liquid nitrogen. Tissue samples of approximately 0.5 gm. were ground in a pre-frozen mortar and pestle, weighed, and immediately diluted to approximately 8 to 10 volumes of iced cold Perchloric acid (6 per cent w/v) and the samples for glycogen determination read on a Perkin Elmer Coleman 55 Spectophotometer at 340 nm.[18] Protein content was modified for use for acid tissue homogenates by Lowry's Folin phenol reagent method. The water content (wet weight to dry weight ratio) was determined by obtaining 200 mg. of left ventricular myocardium and immediately weighing the tissue following termination of the experiment following which it was dried at

*By assuming a left ventricular spherical model rather than a prolate spheroid of identical volume (major-minor axis of 2.1), the base-to-apex fiber length is equal to the circumferential diameter. The relative error between the two systems of calculating force is 8 per cent.

†Since no geometric model is capable of duplicating exact ventricular dimensions, the accuracy of assuming a model for force calculations implies the comparison of relative, rather than absolute values.

Table I Total body and myocardial composition changes in canine protein-calorie malnutrition

	Total body				Ventricular myocardium				
	Number experiments	Weight (Kg)		Weight loss (%)	Weight (Gm.)	Glycogen (µmoles/Gm. dry wt.)	Protein (mg./Gm. dry wt.)	Glucose (µmoles/Gm. Tissue)	Wet/Dry§
		Initial	Final						
I Controls	8	11.8 ± 0.2*	–	–	66.8 ± 1.3	13[illegible] ± 6.9	[illegible]81.2 ± 30.8	8.13 ± 0.67	4.3 ± 0.[illegible]
II Protein-calorie malnutrition	11	11.7 ± 0.3	6.8 ± 0.2	42.1 ± 0.9	47.5 ± 1.4	58.6 ± 10.5	714. ± 17.5	4.38 ± 0.95	5.7 ± [illegible]
Significance†		NS‡	–	–	p < 0.003	p < 0.005	p < 0.0005	NS‡	p < 0.[illegible]

*Mean standard error of the mean.
†I vs II Student t test for unpaired data.
‡NS = not significant.
§Wet/Dry = wet weight divided by dry weight.

Table II Free amino acid concentration in canine left ventricular myocardium

	Controls (n = 3)	Protein-calorie malnutrition (n = 4)	p
Amino acid			
Taurine	43669 ± 10493	44000 ± 664	(NS)
Aspartic acid	2344 ± 30	2471 ± 6[illegible]0	(NS)
Threonine	3570 ± 511	3112 ± [illegible]66	(NS)
Serine	3440 ± 1046	2500 ± 318	(NS)
Glutamic acid	14926 ± 1138	17074 ± 3116	(NS)
Glutamine	62894 ± 687	6154 ± 96[illegible]	(NS)
Citrulline	2718 ± 291	2781 ± 4[illegible]8	(NS)
Glycine	2834 ± 356	2634 ± 200	(NS)
Alanine	22534 ± 3569	25914 ± 6046	(NS)
Valine	662 ± [illegible]6	1212 ± 328	(NS)
Methionine	515 ± 27	638 ± 91	(NS)
Isoleucine	[illegible]33 ± 36	715 ± 69	(NS)
Leucine	839 ± 40	1294 ± 402	(NS)
Tyrosine	340 ± 23	494 ± 48	p < 0.0[illegible]
Phenylalanine	436 ± 20	774 ± 103	p < 0.025
Ornithine	275 ± 65	451 ± 92	(NS)
Lysine	1550 ± 247	2212 ± 392	(NS)
Histidine	1492 ± 84	1278 ± 68	p < 0.05
Arginine	1773 ± 165	1667 ± 36[illegible]	(NS)
1-methyl histidine	–	614 ± 122	Highly
Anserine	3194 ± 122	3697 ± 586	(NS)
Carnosine	2641 ± 120	2569 ± 418	(NS)
Urea	14665 ± 2107	5758 ± 10[illegible]	p < 0.05

*Concentrations (µMoles/mg. dry wt. tissue ± SE.

70°C. for 12 hours, desiccated to room temperature and weighed again.

Tissue-free amino acid contents were obtained following tissue homogenation in 8.3 per cent sulfosalicylic acid (approximately 1,000 mg. of tissue for each mL of sulfosalicylic acid). The samples were then neutralized and assayed on an automated amino acid analyzer (Durrum No. D500).

Morphologic studies. Ultrastructural and morphologic evaluation of myocardial biopsies was carried out in seven control and six experimental dogs.

Immediately following excision of a tissue specimen for biochemical analysis, an additional block of the right ventricular free wall weighing 500 to 600 mg. was rapidly removed, minced in 1 mm. pieces and fixed with cold 6 per cent glutaraldehyde in 0.1 M cacodylate buffer (pH 7.3 to 7.4) overnight. The tissues were then washed with several changes of 4 per cent sucrose in 0.1 M cacodylate buffer; tissues were postfixed with cold 1 per cent osmium tetroxide in 0.1 M cacodylate buffer for 1 hour, dehydrated with a graded series of ethanols and propylene oxide, and embedded in Luft's Epon[15] using flat embedding molds for proper orientation. For purposes of orientation, 0.5µ sections were cut and stained with alkaline toluidine blue and examined by light microscopy. Areas containing myofibers cut in cross-sections as well as longitudinally were selected. Ultrathin sections obtained from these areas with aqueous uranyl acetate and lead citrate and examined with an RCA EM 3G or Siemens Elmiskop I electron microscope.

Diameter of myofibers was measured in Epon embedded, semithin sections (0.5µ) stained with toluidine blue. For this purpose, myofibers cut in cross-section were chosen. Diameters were measured by light microscopy using a calibrated ocular micrometer. A total of 25 myofibers were measured by random selection of five cells in each of five different high-power microscopic fields (40 × objective). The only criterion for selection was that the measured cells represented as closely as possible cross-sections of myofibers.

Interstitial edema, that is, accumulation of

Table III Hemodynamic effects of protein-calorie malnutrition at increasing LV intracavitary volumes

LV volume (ml.)	Control (n = 8) Peak LV pressure (mm. Hg)	LVEDP (mm. Hg)	LV dp/dt max (mm. Hg/sec.)	Protein-calorie malnutrition (= 11) Peak LV Pressure	LVEDP	LV dp/dt
3	89.1 ± 9.4	0	2148 ± 359	80.8 ± 11.9(NS)‡	3.6 ± 0.5(NS)	1459 ± 225(NS)
6	149.4 ± 9.0	1.6 ± 0.8	2687 ± 268	118.0 ± 11.3(p 0.06)	14.8 ± 7.2(NS)	1986 ± 260(p < 0.05)
9	168.7 ± 9.7	4.9 ± 1.7	3337 ± 318	148.5 ± 11.5(NS)	25.4 ± 7.1(p < 0.01)	2441 ± 308(p < 0.05
12	179.4 ± 4.7	10.6 ± 2.8	3492 ± 264	165.9 ± 11.8(NS)	33.3 ± 4.5(p < 0.003)	2733 ± 340(NS)
15	191.0 ± 4.6	20.7 ± 3.5	3929 ± 394	178.5 ± 10.6(NS)	39.0 ± 4.2(p < 0.0025)	2960 ± 405(NS)
18	188. ± 3.6	27.8 ± 3.8	3781 ± 392	174.5 ± 8.8(NS)	42.3 ± 4.2(p < 0.01)	2685 ± 296(p < 0.025)
21	190.3 ± 4.4	35.0 ± 3.8	3319 ± 291	179.0 ± 7.5	46.9 ± 4.8	2699 ± 296(NS)

*Standard error of the mean.
NS = Not significant.
‡I vs. II, Student's t test for unpaired data.

edema fluid around and inbetween myofibers, were estimated histologically in the same biopsy material. The following scores were assigned 0 no edema 1+ mild edema, 2+ moderate edema and 3+ marked edema. The experimental protocol that applied to each individual myocardial biopsy was unknown to the observer who performed the morphometric determinations and estimated severity of interstitial myocardial edema.

Results

I *Nutritional and biochemical changes.* The animal-to-animal variation within the control group was quite small (Table I) in body weight, left ventricular weight, and right ventricular myocardial concentrations of glycogen, protein, and glucose. The dogs subjected to a nitrogen and calorie-poor diet were observed to remain active, alert, and responsive until approximately 40 per cent of initial body weight had been lost. Beyond this point, animals would become quite lethargic and four animals in the initial starting group succumbed of overwhelming sepsis prior to obtaining hemodynamic measurements. In the four animals who died of starvation, consistent findings on postmortem examination included fatty infiltration of the liver ascites, marked interstitial edema in skeletal muscle presumably on the basis of hypoproteinemia, and all of the animals and severe changes of bilateral bronchopneumonia and hemorrhagic enterocolitis.

The average weight loss in the animals who survived long enough to have the hemodynamic studies performed was 4 1 ± 0.9 per cent of initial body weight. On physical and postmortem examinations, these animals demonstrated the changes noted above and the absence of any subcutaneous fat stores. There was a marked reduction in myocardial glycogen content (Table I) without a concomitant change in tissue glucose concentrations. There was a relative increase in protein concentration in PCM hearts compared with controls, although this was apparent only when expressed in terms of dry weight, presumably due to the paucity of non-protein substances such as glycogen. The hearts were grossly edematous as reflected by an increase in the wet/dry ratio (Table I)

Free amino acid concentrations in LV myocardial samples from three control and four PCM animals were measured (Table II). Although few of the changes in individual amino acid concentrations were significant, amino acid concentrations were increased generally in those hearts subjected to PCM compared with controls. The changes in phenylalanine and tyrosine were significantly greater in PCM dogs, and decreased concentration in free histidine was observed in PCM animals, possibly related to increased 1 methylhistidine resulting from the marked catabolic state in these animals. Free urea concentrations were also significantly increased in PCM dogs.

II *Hemodynamic changes* Within the limitations of the experimental model and the range of intraventricular (balloon) volumes utilized to determine the LV response at varying loads, the eight control animals exhibited consistent baseline normal LV function (Table III) Peak

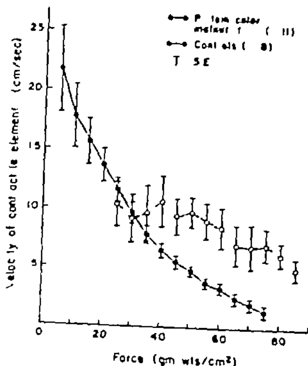


Fig. 2. Force-velocity relations of normal and protein-calorie malnutrition dogs. Group values were obtained after determining the velocity of contractile element in each individual experiment at 5 Gm.-weight intervals and obtaining the arithmetic mean of such points.

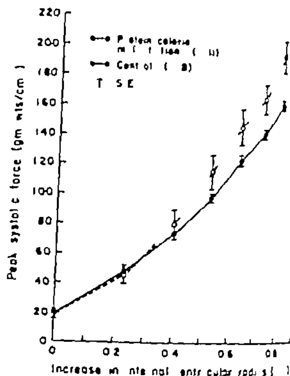


Fig. 3. Group length-tension (force) curves in the control and experimental groups. Data points were obtained as described in *Fig. 2.*

developed LV pressure and LV dp/dt were depressed in PCM dogs when compared with the normally fed animals.

When the force-velocity relationship was compared, however, it was observed that although the maximum developed velocity (Fig. 2) was markedly less in PCM dogs compared with controls, the peak developed force as calculated by the Laplace equation *(vide supra)* was actually *greater*.

The Frank Starling relationship of the left ventricle as expressed by the length tension curve (Fig. 3) revealed lower developed peak systolic force in malnourished dogs compared with controls at each increment of preload. A decrease in LV compliance (Fig. 4) was observed by consistent increase in LV end-diastolic pressure (LVEDP) at each increment of end-diastolic volume.

III. *Morphologic studies*

Light microscopy. Two basic histologic changes were observed: myocardial atrophy and interstitial edema. This combination gave a characteristic appearance to the myocardium: thin slender myofibers present in an expanded extracellular space. This impression was confirmed by the measurement of a mean myofiber diameter of 24.1 ± 0.5μ compared to a diameter of 30.4 ± 0.4μ in control animals (Table IV). Similarly the mean histologic score for interstitial edema was 2.0 ± 0.4 in malnourished dogs and only 0.4 ± 0.1 in control dogs (Table IV). No other changes were observed by light microscopy. There was no perceptible interstitial fibrosis.

Electron microscopy. Except for confirmation of the light microscopic findings, ultrastructural studies were not revealing. Frequently the edema fluid present outside cells resembled the appearance of the plasma seen in the lumen of nearby capillaries. Cytoplasmic structures were generally well preserved with only an occasional nonspecific change such as minor disruption of mitochondrial cristae, occasional lipid droplets, and rare myelin figures. Sarcomeres, sarcoplasmic reticulum, and plasma membranes were structurally intact.

Discussion

These experiments, representing a preliminary investigation into the influence of specific dietary deficiencies on cardiac structure and function

Table IV Morphometric evaluation of myocardium in protein-calorie malnutrition

	No.	Myofiber diameter* (μ)	Interstitial edema (mean score)‡
I. Controls	7	20.4 ± 0.4	0.4 ± 0.1§
II. Protein-calorie malnutrition	6	24.1 ± 0.5§	2.0 ± 0.4
Significance†	–	$p < 0.001$	$p < 0.005$

*Based on histologic measurement of 25 randomly chosen myofibers cut in cross-section per dog.
‡Histologic score (0 to + + +) estimated in plastic-embedded, 0.5μ sections.
§Mean ± standard error of the mean.
†I vs II, Student t test, unpaired data.

have resulted in the observation that PCM adversely affects the dog heart. Although these results would appear to be "obvious" in retrospect, the recognition that the general nutritional state of an organism is an important variable and possible determinant of myocardial function has heretofore not been seriously considered.

There has been ample evidence to support the notion that the myocardium is nearly "omnivorous" in its capacity to utilize a wide variety of substrate sources for energy production, and that it is this capacity to shift preferential food substances which serves as a "fail-safe" system to ensure a constant energy supply to the heart to sustain its metabolic needs. That is, not only is the heart able to utilize glucose, lactate, pyruvate, and glycogen[16] in addition to its preferred diet of lipid, [19] but during states of starvation (and, hence, exogenous nutrient devrivation) Ko and Paradise[20] observed in rats subjected to subacute starvation accumulation of endogenous substrate (glycogen and triglycerides) in myocardium and felt that these substances were able to maintain contractility within the normal range when isolated strips of rat atria were electrically stimulated *in vitro*. These and other experiments in which small, hypermetabolic mammals (rats, guinea pigs, etc.) served as experimental models for human protein-calorie malnutrition are only doubtfully similar enough to larger mammals to have potential clinical significance. After as brief a period of time as four days, for example, many rats subjected to total starvation will succumb of inanition. During prolonged states of human starvation, the role that cardiac dysfunction may play has not been elucidated and most of the

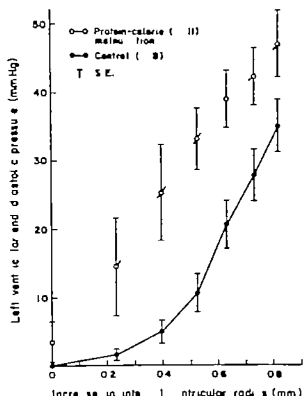


Fig. 4. Pressure-volume (end-diastolic left ventricular internal radius) curves in which significant decreases in left ventricular compliance are noted in the protein-calorie malnutrition dogs.

deaths are associated with terminal generalized sepsis.

Epidemiologic studies of undernourished populations are insufficient as even retrospective models since protein-calorie malnutrition is never "pure" in its naturally-occurring state and is nearly always associated with deficiencies of specific vitamins, most notably thiamine. Beri-beri heart disease, as originally described by Wenckebach,[21] is a form of hypermetabolic, "high-output" cardiac decompensation, except during its final stages when cardiac dilatation and irreversible congestive heart failure occur. Interstitial and perivascular edema followed by myocardial fibrosis and necrosis have been observed in patients dying with beri-beri heart disease.[22] The model used for the present experiments specifically excluded beri-beri as an etiologic factor related to the cardiac dysfunction observed.

Another syndrome of chronic, edematous heart failure reported in malnourished Bantus and Ceylonese[7, 23] is thought to be a nutritional form of heart disease other than thiamine deficiency.



Fig. 5. A and B. A. Normal ppearance of myofibers in control dogs (Epon-embedded section stained with Toluidine blue, original magnifi tion ×385). B. Biopsy of right ventricular myocardium in a dog ith protein-calorie malnutrition. In comparison with the control myocardium, there is marked interstitial edema and moderate cell atrophy (Epon-embedded section stained with Toluidine blue; original magnification ×385).



Fig. 6. Electron micrograph of canine myocardium in protein-calorie malnutrition. Note that the material present in the edematous interstitial space *(IS)* resembles that contained within the lumen of capillaries *(C)*. Myocardial cells have preserved ultrastructure with only minor, non-specific changes such as occasional lipid droplets (Original magnification ×6000).

since thiamine repletion alone did not improve survival or the clinical status of afflicted patients. These patients were observed to have severe hepatic dysfunction with portal fibrosis, hypertension, and fatty infiltration.[28, 29] This hepatic disease is associated with hypoproteinemia, and was hypothesized as the precursor of the cardiac abnormalities. The hearts in these fatal cases were noted to be dilated and hypertrophied with only minute foci of myocardial fibrosis.[29] From these clinical, postmortem, and epidemiological studies, therefore, direct myocardial structural and functional injury due to malnutrition alone was unable to be separated from the indirect and terminal cardiac effects of end-stage liver disease, presumably associated with profound hypoproteinemia. Functional assessments of cardiac performance were not available in these studies so that the sodium and water retention of hypoproteinemia possibly associated with peripheral vascular collapse and terminal sepsis could not be ruled out specifically as the cause of death, rather than primary cardiac failure due to intrinsic defects in contractility.[29]

The present experiments confirm that during prolonged states of protein-calorie malnutrition, marked myocardial *atrophy* occurs, a situation analogous to every other organ in a malnourished organism. Since myocardial *hypertrophy* requires active protein synthesis, it is not surprising that atrophy would be seen in either an experimental model or in prolonged states of nutritional inadequacy even in the face of marked valvular heart disease, as noted by Keys and associates[17] and by Uehlinger[4] in which patients with end-stage valvular heart disease exhibited ur

myocardial atrophy rather than hypertrophy The increase in myocardial water content associated with the morphologic observations of interstitial edema in the present experiments confirms the significant role of edema as a consequence of protein calorie malnutrition.

There is some analogous information which may be inferred from a human clinical model of protein-calorie malnutrition, namely the therapeutically-starved morbidly obese patient. These individuals have been subjected to total protein calorie abstinance but with adequate assurance of preventing hypovitaminoses and electrolyte imbalance by appropriate repletion of these substances as guided by frequent laboratory monitoring. Garnett and co-workers reported a sudden death as a consequence of therapeutic starvation in an obese, but otherwise well, 20-year-old woman. Prior to her death from ventricular fibrillation, the electrocardiogram exhibited low voltage and prolonged Q-T intervals in the presence of normal serum potassium and calcium concentrations. At autopsy the heart was dilated, but weighed only 250 grams. It is possible that the low voltage on electrocardiogram had resulted from intramyocardial edema, since the appearance and size of the heart was similar to those observed in our experimental animals. An over all decrease in heart weight in children dying of malnutrition was also observed by Alleyne and workers and may correspond with the ecrease in heart size reported in fasting humans. n short term fasts, however these changes may be due to a decreased plasma volume and total body sodium content.

The use of an isovolumetric left heart preparation to study the hemodynamic state of these animals was initially employed to compare changes in the force-velocity relationship specifically Since the method of calculating myocardial wall tension using the Laplace equation is based on the left ventricular weight in calculating the estimated external ventricular radius, the apparent discrepancy in the calculated force (wall tension) can be easily explained. Because of the myocardial atroph produced in these *animals*, at similar intraventricular balloon volumes (internal ventricular radius) the external entricular radius would be smaller in the PCM dogs compared with the controls. The wall of the spherical model applied in PCM dogs would be thinner than in the control animals At similar intraventricular pressures, therefore, there would be greater wall tension in the atrophied hearts, a fact which was consistently observed as a decreased peak left ventricular pressure but an *increased* developed force in malnourished hearts compared with controls (Table III, Fig. 2). Since peak developed LV tension is one of the major determinants of myocardial oxygen consumption it is interesting to speculate that such a mechanism might conceivably be of clinical significance in malnourished patients with ischemic heart disease.

The analyses of free amino acid concentrations in myocardium reported above are difficult to interpret since there have been few previous experiments in which such studies are available for any tissues other than plasma itself. The presence of 1 methyl histidine is not surprising and has been valuable as it serves as a marker of profound catabolism. The observed increase in concentration of free amino acids is most likely a reflection of the decrease in non-protein substances present in this myocardium compar[ed] with controls, since we expressed our results [in] terms of dry weight of tissue analyzed. Anoth[er] possible explanation would be a lack of endogenous protein synthesis locally within the myocardium because of the absence of suitable substrat[e] No specific deficiencies of essential amino acid were identified in these animals. The amino acid content of myocardial protein itself was no[t] analyzed since it would be predicted that the genetic coding for specific amino acids sequence in myocardial proteins would not be altered by systemic alterations of substrate availability In the absence of suitable amino acids for protein synthesis, one would have predicted the absence of synthesis, as we did observe indirectly rather than the accumulation of available, but non-utilized amino acids.

In a prospective clinical study of the usefulness of immediate postoperative hyperalimentation (total parenteral nutrition) in patients suffering from cardiac cachexia we observed an increased morbidity and mortality compared with non malnourished patients with similar diseases undergoing similar operations. The addition of nutritional support techniques following the operations was not beneficial in ameliorating these adverse effects. Blackburn and co-workers have suggested an aggressive preoperative program of nutritional support consisting of high-

density enteral feedings combined with intravenous support when indicated. They determined that significant indices of malnutrition existed in such patients as reflected by anthropomorphic measurements and decreased delayed hypersensitivity responses. They hypothesized that this type of nutritional support program might lessen the operative risk of these patients who are about to undergo palliative open-heart surgery.

The experimental animals reported above started with initially normal hearts and were subjected to diets which resulted in protein-calorie malnutrition. Whether or not this is an analogous situation to an abnormal heart, either fibrosed due to ischemic heart disease or hypertrophied due to valvular heart disease or hypertension, subjected to similar nutritional inadequacies, is a matter of speculation. The marked changes in left ventricular compliance and in intrinsic contractility itself observed in these experiments, however, raise certain questions regarding the influence of human malnutrition on cardiac performance.

It would seem rational to advocate nutritional support in markedly malnourished patients on the basis of non-cardiac factors alone. In light of the present observations, however, particularly when cardiac decompensation is present concomitantly, it would be interesting to conduct clinical trials to determine if there would be improvement in cardiac function associated with refeeding of starved and depleted patients.

Summary

In the absence of thiamine deficiency, the specific effects of protein-calorie malnutrition on left ventricular (LV) function are unknown. Mature beagle dogs of both sexes were subjected to a hypocaloric, nitrogen-poor diet which resulted in a weight loss of approximately 40 per cent after seven weeks. Following preparation of this nutritional model, myocardial contractility was assessed acutely by obtaining isovolumetric LV contractions on cardiopulmonary bypass at constant heart rate, mean aortic pressure, and at a wide range of end-diastolic volumes. These changes were compared to a matched group of animals which were normally fed. There were consistent decreases in LV compliance in malnourished animals compared with normals. Indices of ventricular contractility per se (LV dp/dt, force-velocity relations, peak developed LV pressure) were also diminished in the experimental animals. Myocardial concentration of glycogen was diminished in malnourished compared to control animals. Light and electron microscopic examination confirmed the presence of myofibrillar atrophy in the presence of interstitial edema. These results suggest that protein-calorie malnutrition seriously interferes with normal LV function in the experimental animal by reducing compliance as a result of "starvation edema," and by reducing myocardial contractility associated with atrophy of the myofibers.

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Coronary reperfusion Effects of hyperosmotic mannitol

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Coronary blood flow diminishes on reperfusion of acutely ischemic myocardium due to an increase in coronary vascular resistance. While the mechanism responsible for the elevated coronary resistance is unclear intracellular and interstitial edema that accompany ischemia and reperfusion have been implicated.[1-4]

Hyperosmotic mannitol has been reported to increase coronary blood flow and improve cardiac function during acute myocardial ischemia, and also to reduce infarct size during coronary occlusion. Willerson and associates[11] observed that mannitol reduced the initial coronary resistance upon reperfusion after release of a temporary coronary artery occlusion.[11] Powell and colleagues[4] also reported that mannitol reduced coronary vascular resistance during brief reperfusion following acute myocardial ischemia. These beneficial effects of mannitol during reperfusion may be due to its ability to reduce ischemic cell swelling or to directly relax vascular smooth muscle.[12]

While mannitol has been demonstrated to augment blood flow in the early stage of coronary reperfusion no investigations have examined the ability of mannitol to attenuate the progressive increase in coronary vascular resistance that accompanies prolonged reperfusion. Hence, the purpose of this study was to evaluate the effects of hyperosmotic mannitol on coronary hemodynamics, cardiac function, and the regional distribution of myocardial blood flow during an extended period of coronary artery reperfusion.

Methods

Experimental preparation Experiments were conducted in 16 adult mongrel dogs weighing 17 to 30 kilograms. The animals were anesthetized with sodium pentobarbital (33 mg./Kg., intravenously) Additional anesthetic was administered as required to maintain a stable anesthetized state. Endotracheal intubation was carried out and the lungs were ventilated with room air by a positive pressure respirator (Harvard 614) Systemic arterial blood gases and pH were kept within normal physiological limits by adjusting the respirator

Aortic blood pressure was measured through a vinyl cannula inserted in the left common carotid artery and advanced into the aortic arch. A cannula was also positioned in the abdominal aorta (via a femoral artery) for collecting arterial blood samples. A left thoracotomy in the fourth intercostal space was performed, and the pericardium was incised to expose the heart. Vinyl cannulas were placed in the left atrium and left ventricle (via the left atrial appendage) for administering radiolabelled microspheres and for measuring left ventricular pressure, respectively The left circumflex (LC) and left anterior descending (LAD) coronary arteries were isolated approximately three centimeters from their

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origin. Electromagnetic flow transducers (Micron RC1000) were positioned on the LC and LAD coronary arteries and snare ligatures were placed around each artery approximately five millimeters distal to each flow transducer

Regional myocardial contractility was measured with two Walton Brodie strain gauge arches with adjustable feet (John A. Warren P O Box 412, Charleston, South Carolina, 2940?) secured to the myocardium in the region perfused by the LAD coronary artery Contractile force of the superficial and deep fibers were separated by orienting gauges parallel to the fibers under study Contractile force of the deeper fibers was obtained with a gauge modified by attaching a 1 5 centimeter length of 18 gauge hypodermic needle perpendicular to each foot. The distance between the feet of each strain gauge was adjusted so that the myocardial segment between them was stretched by about 30 per cent of its initial length.

Arterial hematocrits, serum osmolalities, and blood gases were measured periodically throughout the experiment. Serum osmolality was measured with a vapor pressure osmometer (Wescor 5130) having a precision of ± 3 mOsm./Kg. Arterial blood gases and pH were measured with an Instrumentation Laboratory 113-S1 blood gas analyzer Measured hemodynamic variables were recorded on a multi-channel oscillograph (Hewlett Packard 7784A)

Minimal resistance in the reperfused vascular bed was determined by intermittent 90-second occlusions of the LAD since such occlusion induced maximal coronary vasodilation. The minimal coronary vascular resistance during a reactive hyperemia was calculated as a ratio of the mean aortic blood pressure to the peak coronary blood flow following release of the 90-second LAD occlusion.

Regional myocardial blood flows were determined with nine μ diameter radiolabelled microspheres (3M Co) injected into the left atrium [14] Prior to administration, the microspheres were dispersed by alternate agitation in an ultrasonic bath and a vortex mixer Approximately 5×10^6 microspheres were administered for each flow determination and were flushed into the left atrium with approximately three milliliters of body temperature saline By using microspheres labelled with three different radionuclides (Ce ^{85}Sr and ^{46}Sc) it was possible to make multiple determinations of myocardial blood flow in each animal. Beginning simultaneously with each microsphere administration, arterial blood was collected at a constant rate for three minutes, so that regional myocardial blood flow in ml./min./g. could be computed by the procedure described by Makowski and associates. and by Buckberg and colleagues. Essentially this procedure involves computing the number of milliliters of arterial blood of known radioactivity required to pass through each gram of tissue to account for the radioactivity measured in that tissue.

Upon terminating the experiment, the heart was excised and frozen to facilitate sampling. Tissue samples were obtained from the normal or control region supplied by the LC, and the reperfused region supplied by the LAD The samp were divided visually into epicardial, mid-mur and endocardial layers for measurement of tra mural myocardial blood flow The samples we weighed and analyzed for radioactivity in multi-channel gamma counter (Packard Instrument Co. 9016). Isotope separation was accomplished by standard techniques of gamma spectroscopy with the aid of a minicomputer (DE PDP/8E).

Cardiac arrhythmias, mainly ventricular in origin, were frequently observed to accompany the occlusion and reperfusion of the LAD To minimize the occurrence of these arrhythmias, lidocaine (1 mg./minute) was infused throughout the experiment. This dosage of lidocaine caused no significant hemodynamic effects.

Experimental procedure. Following stabilization of the preparation, control hemodynamic measurements were obtained. The snare ligature on the LAD was then tightly secured and the coronary artery was occluded for two hours. This occlusion rendered ischemic approximately 30 per cent of the left ventricular free wall. Reperfusion of this region was accomplished by releasing the snare ligature

An infusion of hyperosmotic mannitol (9.2 ml./minute, 25 per cent solution) was begun minutes before release of the LAD occlusion and continued during two hours of coronary reperfusion. The initial infusion rate of mannitol was maintained until serum osmolality increased by approximately 40 mOsm./Kg. The infusion rate was then adjusted to maintain serum osmolality

Table I Hemodynamic effects of infusing hyperosmotic mannitol during reperfusion following 2 hours of LAD coronary artery occlusion (n = 16)

	Control	*Reperfusion*						
	Pre-occlusion	*Initial*	*5 min.*	*15 min.*	*30 min.*	*60 min.*	*90 min.*	*120 min.*
AoP (mm. Hg)	121	137*	138*	129	126	121	113	113
	±4	±5	±5	±5	±6	±6	±4	±5
LVEDP (mm. Hg)	5	11	10*	8	8*	7*	7*	6
	±.7	±1.1	±1.5	±1.2	±1.0	±1.0	±.9	±.9
HR (beats/min.)	164	137*	138*	139*	143*	145	153	150
	±5	±7	±6	±6	±6	±8	±7	±6
Hct	38	34	31	30*	32*	35	37	39
	±2	±2	±2	±3	±2	±2	±2	±2
Osm (mOsm./Kg.)	299	336	339	342	343	341	343	360
	±4	±6	±5	±6	±5	±5	±5	±5

AoP = aortic pressure; *LVEDP* = left ventricular end-diastolic pressure; *HR* = heart rate; *Osm* = serum osmolality; *Hct* = hematocrit. Values are mean ± SE.

* = $P < .05$ vs. control.

at this level during two hours of LAD reperfusion. An average of 418 milliliters of hyperosmotic mannitol was infused during the course of the experiment.

Statistical analyses of the data were accomplished using the Student's t test modified for paired observations. Statistical comparison of these data and those of a previous study were carried out using the unpaired Student's t test. Results were considered significant when $P < 0.05$.

Results

Hemodynamic findings. Changes in systemic hemodynamic parameters during coronary reperfusion accompanied by hyperosmotic mannitol infusion are presented in Table I. Serum osmolality was elevated during reperfusion and remained relatively constant during the two hour period of mannitol infusion. The arterial hematocrit decreased during the initial period of reperfusion when mannitol was infused at a rapid rate. However after one hour of reperfusion, the hematocrit returned to control.

Aortic pressure was greater than the pre-occlusion control value when LAD reflow was initiated, and at five minutes of reperfusion. After 15 minutes of reperfusion, aortic pressure had returned to control and remained unchanged for the duration of the mannitol infusion. Left ventricular end-diastolic pressure was elevated upon release of the coronary occlusion but gradually returned toward control during reperfusion. Heart rate was less than control when coronary blood flow was reestablished but returned to control by 60 minutes of reperfusion.

Coronary resistances for the reperfused LAD and normal LC vasculatures were calculated as a ratio of mean aortic pressure to the respective mean coronary blood flow. The effects of mannitol on coronary resistances during reperfusion are illustrated in Fig. 1. Upon initiating reperfusion resistance in the LAD decreased 71 per cent from the control pre-occlusion value. As reperfusion continued, LAD vascular resistance rose progressively in spite of the mannitol infusion, increasing by 37 per cent at two hours of reperfusion. Coronary resistance in the LC decreased 36 per cent from control when LAD flow was reestablished, but it returned to control by 15 minutes of reperfusion and remained unchanged thereafter. In nine of the animals in this study the period of reperfusion was extended for an additional two hours after the mannitol infusion was terminated. At four hours of reperfusion, serum osmolality was 329 mOsm./Kg. and coronary resistance in the reperfused LAD vasculature was 8.1 ± 1.5 mm. Hg/ml./minute or 45 per cent above control. Coronary resistance in the normal LC vasculature was 3.9 ± 0.6 mm. Hg/ml./minute and not different from control.

The changes in minimal LAD vascular resistances during four hours of reperfusion are presented in Fig. 2. Minimal resistance was 22 per

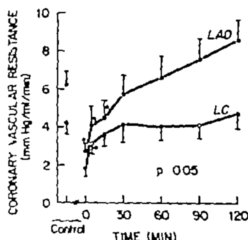
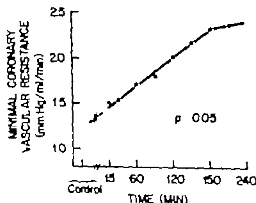


Fig 1 Coronary resistance in the left anterior descending (LAD) and left circumflex (LC) vascular beds before LAD [illegible]usion (control), and during 2 hours of LAD reperfusion accompanied by mannitol infusion. Values are mean and one standard erro[r]



[F]ig 2 Minimal coronary resistance (aortic pressure/peak reactive hyperemic flow) in the left anterior descending coronary artery vascular bed before LAD occlusion (control), and during 4 hours of coronary reperfusion. Mannitol was infused during the first 2 hours of reperfusion

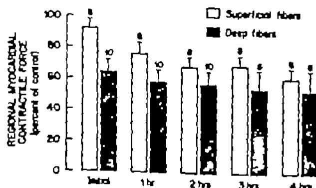


Fig 3. Myocardial contractility in the superficial and deep fibers of the reperfused region during 4 hours of coronary reperfusion. Mannitol was infused during the first 2 hours of reperfusion. Values are mean and one standard error. *Numbers above bars* indicate number of animals

cent and 63 per cent greater than control after 15 minutes and two hours of reperfusion, respectively. At four hours of reperfusion, minimal resistance had increased by 96 per cent. The minimal LAD resistance increased progressively for the first three hours of reperfusion and plateaued during the last hour of reflow at a level approximately two times that of control.

Regional myocardial blood flow The transmural distribution of myocardial blood flow in the left ventricle during reperfusion is presented in Table II. Blood flows to the normal and reperfused regions at five minutes of reperfusion were similar and were greater than values reported for normal, non reperfused hearts.[14] No significant transmural gradient of blood flow was observed in either region of the left ventricle following five minutes of reperfusion.

After two hours of reperfusion, myocardial blood flows to the normal and reperfused regions were significantly less than their corresponding values at five minutes of reperfusion. However, blood flow in the reperfused region declined more than did flow in the normal region. In addition, myocardial blood flow in the reperfused region showed a transmural gradient of flow favoring the subepicardial layer (endo/epi ratio = 0.72) while the normal region showed a uniform transmural blood flow distribution

Following four hours of reperfusion, myocardial blood flows in the reperfused region were further decreased. Blood flows in each of the transmural layers was significantly less than that observed at two hours of reperfusion. The transmural gradient of blood flow favoring the subepicardium became steeper (endo/epi ratio = 0.44)

Regional contractile function Contractile function in the left ventricular region perfused by the LAD coronary artery decreased markedly or was abolished completely following LAD occlusion. Upon reperfusion, regional contractile function returned in some animals but remained absent in others.

Contractile function in the deep myocardial fibers of the reperfused region was measured in 16 animals. Six animals exhibited persistent systolic bulging of the reperfused ventricular region during reflow while the remaining 10 animals showed contractile behavior. Changes in myocardial contractility in the reperfused region are presented in Fig. 3. Among those animals demonstrating a return of regional function, contractil-

Table II Regional myocardial blood flows (mL/min./g.) at 5 minutes, 2 hours and 4 hours of LAD reperfusion. Hyperosmotic mannitol was infused for the first 2 hours of reperfusion

	Normal region			*Reperfused region*		
Reperfusion period	*epi*	*mid*	*endo*	*epi*	*mid*	*endo*
5 minutes‡	1.60 ± .20	1.90 ± .23	1.83 ± .25	1.94 ± .20	1.69 ± .24	1.77 ± .26
2 hours‡	.61 ± .05†	.68 ± .06†	.65 ± .05†	.53 ± .04*†	.38 ± .05*†	.44 ± .06*†
4 hours§	.76 ± .09†	.77 ± .09†	.77 ± .08†	.48 ± .06*†	.24 ± .08†	.52 ± .06*†

epi = epicardium; mid = mid-myocardium; endo = endocardium. Values are mean ± SE.
†P < .05, comparison within regions (2 hrs., 4 hrs. vs 5 min.)
*P < .05, comparison between regions (reperfused vs. normal).
‡16 observations, §9 observations.

ty in the deep myocardial fibers recovered to 64 per cent of the pre-occlusion control value upon initiating reperfusion. After two and four hours of reperfusion, deep fiber contractility diminished to 57 per cent and 53 per cent of control, respectively.

Contractility in the superficial myocardial fibers of the reperfused region was measured in eight animals, all of which exhibited contractile behavior during reperfusion. Upon initiating reperfusion, contractility in the superficial myocardial fibers recovered to 9? per cent of the pre-occlusion control value. Superficial fiber contractility declined progressively to 68 per cent and 61 per cent of control by two and four hours of reperfusion, respectively.

Discussion

This study demonstrates that treatment with hyperosmotic mannitol does not prevent the progressive increase in coronary vascular resistance or the selective underperfusion of the subendocardium during reperfusion following two hours of coronary artery occlusion.

Coronary hemodynamics. The observed dilation of the reperfused vasculature immediately upon reperfusion is in agreement with the findings of other investigators.[11] This vasodilation is likely due to metabolites such as adenosine, lactate, K and H that accumulate during myocardial ischemia. Accompanying coronary reperfusion with the infusion of mannitol did not accentuate this vasodilation.

A progressive increase in resistance in the reperfused vasculature during reperfusion without mannitol treatment has been shown previously. In the present study coronary resistance increased progressively during reperfusion in the presence of mannitol. Comparison of our previous data with those of the present study showed no significant effect of treatment with hyperosmotic mannitol on the progressive increase in coronary resistance during reperfusion.

At four hours of reperfusion, two hours after the infusion of mannitol was terminated, coronary resistance further increased to 45 per cent above control. Comparison of these data with those previously reported showed no significant effect of mannitol treatment. Thus, it appears that elevating serum osmolality with hyperosmotic mannitol did not attenuate the increase in vascular resistance in the reperfused region during prolonged coronary reperfusion.

Coronary resistance in the normal LC vasculature decreased when LAD reperfusion was begun. This decrease in coronary resistance appears to be the result of coronary vasodilation induced by hyperosmotic mannitol, since our previous study showed no change in LC vascular resistance when flow was reestablished in the LAD following two hours of occlusion in the absence of mannitol. It was possible that the hemodilution and resulting decreased blood viscosity produced by the initial rapid infusion of mannitol may have contributed to the decrease in LC resistance. After 30 minutes of reperfusion, LC resistance returned to control and remained unchanged for the duration of reperfusion. This waning of the vasodilator response to mannitol is consistent with the findings of Fixler and co-workers[20] and Krishnamurty and colleagues.[21]

The passive component of coronary resistance is reflected in the minimal resistance to coronary blood flow following release of a 90-second coronary occlusion. An increased passive resistance in the reperfused coronary vascular bed, which is indicative of structural changes, has been reported. Minimal resistance was previously

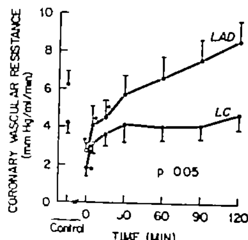


Fig. 1. Coronary resistance in the left anterior descending (LAD) and left circumflex (LC) vascular beds before LAD occlusion (control), and during 2 hours of LAD reperfusion accompanied by mannitol infusion. Values are mean and one standard error.

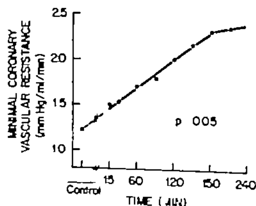


Fig. 2. Minimal coronary resistance (aortic pressure/peak reactive hyperemic flow) in the left anterior descending coronary artery vascular bed before LAD occlusion (control) and during 4 hours of coronary reperfusion. Mannitol was infused during the first 2 hours of reperfusion.

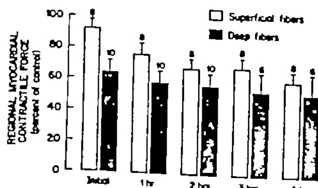


Fig. 3. Myocardial contractility in the superficial and deep fibers of the reperfused region during 4 hours of coronary reperfusion. Mannitol was infused during the first 2 hours of reperfusion. Values are mean and one standard error. *Numbers above bars* indicate number of animals.

cent and 63 per cent greater than control after 15 minutes and two hours of reperfusion, respectively. At four hours of reperfusion, minimal resistance had increased by 96 per cent. The minimal LAD resistance increased progressively for the first three hours of reperfusion and plateaued during the last hour of reflow at a level approximately two times that of control.

Regional myocardial blood flow. The transmural distribution of myocardial blood flow in the left ventricle during reperfusion is presented in Table II. Blood flows to the normal and reperfused regions at five minutes of reperfusion were similar and were greater than values reported for normal, non reperfused hearts.[14] No significant transmural gradient of blood flow was observed in either region of the left ventricle following five minutes of reperfusion.

After two hours of reperfusion, myocardial blood flows to the normal and reperfused regions were significantly less than their corresponding values at five minutes of reperfusion. However, blood flow in the reperfused region declined more than did flow in the normal region. In addition, myocardial blood flow in the reperfused region showed a transmural gradient of flow favoring the subepicardial layer (endo/epi ratio = 0.72) while the normal region showed a uniform transmural blood flow distribution.

Following four hours of reperfusion, myocardial blood flows in the reperfused region were further decreased. Blood flows in each of the transmural layers was significantly less than that observed at two hours of reperfusion. The transmural gradient of blood flow favoring the subendocardium became steeper (endo/epi ratio = 0.44).

Regional contractile function. Contractile function in the left ventricular region perfused by the LAD coronary artery decreased markedly or was abolished completely following LAD occlusion. Upon reperfusion regional contractile function returned in some animals but remained absent in others.

Contractile function in the deep myocardial fibers of the reperfused region was measured in 16 animals. Six animals exhibited persistent systolic bulging of the reperfused ventricular region during reflow while the remaining 10 animals showed contractile behavior. Changes in myocardial contractility in the reperfused region are presented in Fig. 3. Among those animals demonstrating a return of regional function, contractile

Table II Regional myocardial blood flows (mL/min./g.) at 5 minutes, [illegible] hours and [illegible] hours of reperfusion. Hyperosmotic mannitol was infused for the first 2 hours of reperfusion

Reperfusion period	Normal region			Reperfused region	
	epi	mid	endo	epi	mid
5 minutes‡	1.60 ± .20	1.90 ± .23	1.83 ± .25	1.34 ± .23	[illegible]
2 hours‡	.81 ± .05†	.88 ± .06†	.85 ± .05†	.63 ± .07	[illegible]
4 hours§	.78 ± .09†	.77 ± .09†	.77 ± .06†	.48 ± .07	[illegible]

epi = epicardium; mid = mid myocardium; endo = endocardium. Values are mean ± SE.
†P < .05, comparison within regions (2 hrs., 4 hrs. vs. 5 min.).
*P < .05, comparison between regions (reperfused vs. normal).
‡16 observations, §9 observations.

ty in the deep myocardial fibers recovered to 64 per cent of the pre-occlusion control value upon initiating reperfusion. After two and four hours of reperfusion, deep fiber contractility diminished to 57 per cent and 53 per cent of control, respectively.

Contractility in the superficial myocardial fibers of the reperfused region was measured in eight animals, all of which exhibited contractile behavior during reperfusion. Upon initiating reperfusion, contractility in the superficial myocardial fibers recovered to 92 per cent of the pre-occlusion control value. Superficial fiber contractility declined progressively to 68 per cent and 61 per cent of control by two and four hours of reperfusion, respectively.

Discussion

This study demonstrates that treatment with hyperosmotic mannitol does not prevent the progressive increase in coronary vascular resistance or the selective underperfusion of the subendocardium during reperfusion following two hours of coronary artery occlusion.

Coronary hemodynamics. The observed dilation of the reperfused vasculature immediately upon reperfusion is in agreement with the findings of other investigators.[12] This vasodilation is likely due to metabolites such as adenosine, lactate, K+ and H+ that accumulate during myocardial ischemia. Accompanying coronary reperfusion with the infusion of mannitol did not accentuate this vasodilation.

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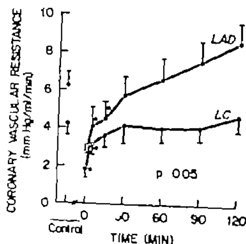


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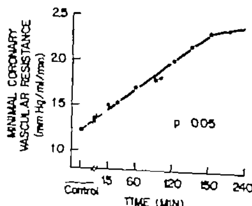


Fig 2 Minimal coronary esistance (aortic pressure peak reactive h peremic flow) in the left anterior descending coronary artery vascular bed before LAD occlusion (control), and during 4 hours of coronary reperfusion. Mannitol was infused during the first 2 hours of reperfusion

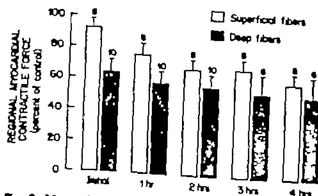


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The single precordial lead for ST segment monitoring Comparison with the multiple lead map

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Providence R. I

The magnitude and extent of ST segment elevation as measured by a multiple lead, precordial map has been found to be sensitive to small degrees of myocardial infarct extension and to correlate well with the ST elevation measured by the epicardial technique. In spite of debate concerning the accuracy and applicability of the precordial mapping technique, it continues to serve as a non-invasive index of myocardial ischemic injury and is considered capable of producing useful information in evaluating the effects of interventions designed to minimize ischemia or to limit infarct size.

Practical considerations, however in the application of the precordial mapping procedure severely limit its use in clinical investigations. The recording of electrocardiographic tracings from a precordial map is time consuming the need for multiple and frequent mapping periods during interventions make it poorly suited to the evaluation of rapidly changing ST elevations, and may furthermore, disrupt patient care routines.

Precordial ST segment data have been obtained using other more easily applied mapping techniques. Madias and co-workers found good agreement between the sum of ST elevation (ΣST) of the precordial map and ΣST of the six standard ECG leads in 15 of 25 patients with acute anterior myocardial infarction, while some disagreement existed between these methods in eight patients, and major disagreement in two patients. Gold and co-workers have used the ΣST in the six standard precordial leads to assess the effect of interventions to reduce ischemia in patients with acute anterior myocardial infarction. With this less complex mapping technique, a significant decrease in ST segment elevation was observed following nitroglycerin and propranolol administration and with the intra-aortic balloon pump.

The use of the vectorcardiogram for evaluation of ST elevation in the acute infarct setting has likewise been considered more easily performed than standard precordial mapping and has been shown in two independent studies to correlate well with a 35 lead precordial technique.[14] Akiyama and co-workers[15] have, moreover reported that a single vectorcardiographic lead may also be used for CCU rhythm surveillance. Nevertheless, the technique requires the application of electrodes to the chest, back and neck, and may not be well suited to routine care or investigation.

This study was, therefore, undertaken to test whether a practical simplification of the precordial mapping technique, namely the use of a *single* carefully selected precordial lead, could provide information concerning ST segment changes comparable to the standard ΣST tech

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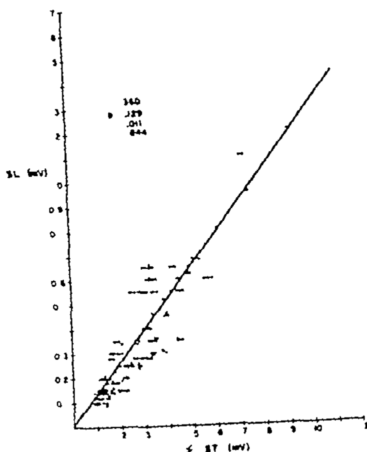


Fig. 1 The ST elevation measured by the single lead (*SL*) and ΣST method at each recording period in each animal studied. The least squares linear regression line for these points is drawn. *a* = y-intercept and *b* = slope of the regression line *n* = number of paired observations, *r* = correlation coefficient.

nique. Pigs were used as the experimental model since coronary occlusion invariably results in infarction in the pig, and the pig's native coronary circulation closely resembles man's. Three groups of animals were studied following coronary occlusion (1) those subsequently having coronary reperfusion, (2) those having infarction extension, and (3) those without a modifying intervention.

Methods

Myocardial infarction was created by a closed chested technique described elsewhere in 31 farm bred pigs anesthetized with sodium pentobarbital and chloralose. In brief a No 8F thin walled catheter was introduced fluoroscopically into the left anterior descending coronary artery (LAD) A No. 3F embolectomy catheter (Edwards Laboratories) was then passed through the larger catheter positioned in the LAD and the outer catheter was withdrawn into the aorta After baseline measurements, the embolectomy catheter balloon was inflated with radio-opaque material to accomplish LAD occlusion. An 18 electrode map was placed subcutaneously over the precordial area and ECG leads were recorded, three at a time, at a paper speed of 25 mm per second at double standard (1.0 mV equal to 20 mm.) Recordings were made at frequent intervals for ST segment analysis.

A control group of nine animals underwent only the initial permanent occlusion. In 12 other animals, reperfusion of the ischemic myocardium was accomplished at 60 minutes by deflation of the coronary occluding balloon and removal of the catheter Extension of infarction was accomplished in an additional 10 animals at 60 minutes by a partial deflation of the occluding balloon, by a partial deflation of the occluding balloon, retraction of the catheter to a more proximal location in the LAD and reinflation of the balloon.

ST segment elevation in each animal was measured 100 msec. beyond the beginning of the QRS complex. Only complexes showing no wide-

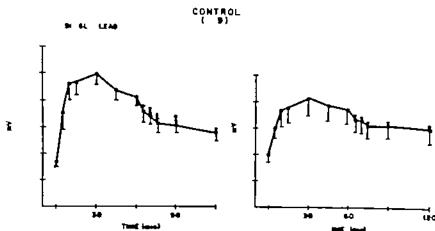


Fig. 2. Mean and standard erro for the ST levation in control animals using single lead *(left)* or ΣST *(right)* analysis. Significance of the level during the second hour compared t the 60 minut value is indicated abov each second hour point. *mV* = millivolt, = $p < 0.01$, = $p < 0.001$.

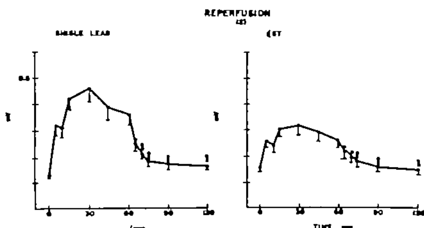


Fig 3. Mean and standard error for the ST elevation in reperfusion animals.

ing of the QRS were used for this measurement. ΣST was derived in standard fashion summing the ST segment elevation in all precordial leads for each recording period. In each animal the single lead (SL) used for comparison with ΣST was identified during the first hour following infarction as the one lead of the precordial map group showing the greatest ST segment elevation. This lead was then followed for the remainder of that study. In the infarct extension group an additional examination of the precordial leads was made following the extension to determine whether the originally identified SL continued to serve as the lead showing greatest elevation.

Statistical analysis. A least squares linear regression of SL versus ΣST was calculated for each animal as well as for the entire group of animals and in this way correlation coefficients were obtained.

Using Student's t test for group data, the ΣST and SL ST elevation changes occurring during the two hours of this study were compared within each group in terms of the time to peak ST elevation following occlusion in the extension group, the time to peak elevation following infarct extension was also compared. Paired t test analysis was used to determine the significance of the change in ST elevation occurring after 60 minutes using ΣST and SL in each group. $p < .05$ was considered the lower limit of statistical significance. Since there was no attempt in the experimental protocols to maintain a similar level of LAD occlusion between the three groups, the absolute height of the ST elevation between the groups was not compared.

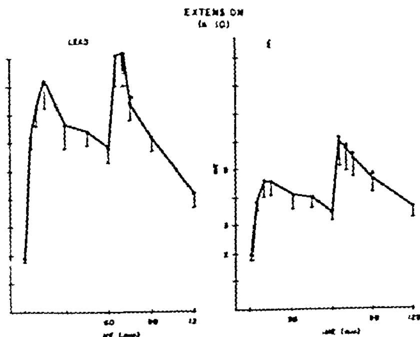


Fig. 4. Mean and standard error for the ST elevation in extension animals.

Results

In the 31 animals studied, ST measurements were made at 560 periods. Each SL determination was plotted against its simultaneously measured ΣST (Fig. 1); the correlation coefficient between these two values was 0.844. The correlation coefficient was also individually determined for each animal; the mean and its standard error of the correlation coefficients for the 31 animals was 0.859 ± 0.03.

When compared statistically, the time to peak ST elevation after occlusion within each group was similar (Control: ΣST 31 ± 6 minutes, SL 22 ± 5 minutes; Reperfusion: ΣST 1 ± 3 minutes, SL 1 ± 3 minutes; extension: ΣST 20 ± 5 minutes, SL 20 ± 5 minute; $p > .05$). In the extension group the time from the pre-extension control (60 minutes) to peak was also similar (ΣST 11 ± 2 minutes, SL 9 ± _ minutes, $p > .05$).

In the control and reperfusion groups the fall of the ΣST and SL curves was analyzed by paired statistical comparison of the 60 minute ST elevation with those occurring subsequently (Figs. 2 and 3). Both ΣST and SL fell to a greater extent in the reperfusion than in the control group. ST by both analyses in both groups achieved a significant drop by 65 minutes and persisted for the remainder of the study. In the extension group (Fig. 4) a similar comparison showed significant rises from the pre-extension control at 65, 70 and 75 minutes in both ΣST and SL. At 90 minutes ΣST remained significantly elevated while SL had fallen to a level similar to that of the pre-extension measurement.

In the extension group, during the post-extension period the single precordial lead showing maximal ST elevation was identified in order to determine its relationship to the original SL. In six of the nine animals, the same SL was maximally elevated under both circumstances; in the remaining three animals, the original SL showed major but not maximal ST elevation. In all three situations it was located immediately adjacent to the lead showing maximal elevation.

Discussion

The analysis of precordial ST segments, while unlikely to provide data on absolute infarct size using the current methods of examination, can produce useful information concerning the relative extent of myocardial injury as well as directional changes associated with therapeutic interventions designed to reduce infarct size. There has been the suggestion that more extensive precordial mapping may provide additional information regarding infarct size. Alternatively, it could be reasoned that the precordial electrodes, placed at some distance from the surface of the heart, are more likely to record the vectoral sum

of electrical activity rather than reflect the electrical activity localized to the area of myocardium beneath them additional precordial lead recordings would therefore provide no more information than this vectoral analysis.[16]

This study was undertaken to determine whether a single precordial lead, placed at the point of maximal ST elevation and monitoring an anteriorly-directed ST vector could provide information comparable to that obtained with multiple electrode mapping. In all three of our experimental protocols, this single lead, selected as the lead with the maximal ST segment elevation during the first hour following occlusion continued to *provide all the direction and amplitude* information contained within the more complex ΣST determination.

In the infarction extension group, the single lead also proved to be a sensitive index of the additional ischemic injury It remained as the lead having the greatest post-extension elevation in six animals while not showing the largest elevation following extension in the remaining three animals, it nevertheless showed definite re-elevation of the ST segment as evidence for the extension. This occurrence may be related to the manner with which the infarct extension was accomplished. the coronary artery was re-occluded at a more proximal location with the additional ischemic involvement located in close proximity to the original area of the infarction. The vectorial direction of the ST segment might, therefore, be expected to change little if at all. The ability of the original single lead to reflect, or even detect additional areas of ischemia would largely depend on the location of that additional ischemia. In practice the suggestion of an increased or new area of ischemia should, therefore, be an indication for reapplication of the entire electrode map and the reanalysis of all leads for selection of a new lead having maximal ST elevation.

With this exception, the single lead precordial electrode appears to be an acceptable alternative to the multiple lead map in acute anterior myocardial infarction. It has the advantage of simplicity of use with minimal interference of patient routine and will allow frequent or even continuous monitoring with minimal observer effort or patient discomfort

Precordial mapping must always be utilized with the recognition that other factors such as pericarditis, electrolyte changes, or alternations in intraventricular conduction may influence ST segment analysis. Decrease in the height of the R wave or development or deepening of Q waves in the same lead as the ST elevation can be considered evidence for permanent tissue damage[4, 13] and can be further used to assess the effects of interventions affecting infarct size. This investigation does not address the analysis of QRS in the single lead, but its application to this task may be considered worthy of further study The single lead, when carefully selected and used with the considerations addressed above, appears to be an accurate index of myocardial injury whose use can *facilitate therapy intended to reduce ST* elevation and can expand clinical studies of acute myocardial ischemic injury

Summary

ST segment elevation, used as an index of the relative extent of myocardial ischemic injury was measured using a single precordial lead located at the point of maximum ST elevation. ST changes were followed for two hours after acute coronary occlusion in pigs, and were compared to the sum of ST elevation recorded with an 18 lead precordial map. Some animals were subjected to Reperfusion (n = 12), others to infarct extension (n = 10) while a control group (n = 9) was followed without an ST-modifying intervention. Correlation between ΣST and ST in the single lead was good, with a correlation coefficient of 0.844 at 360 points of comparison. Time to peak ST elevation using the single lead technique was comparable to that using the 18 lead map. Changes in the ST elevation using both techniques were similarly reduced following reperfusion, increased following extension, and followed a similar downslope pattern in the unmodified infarct group. This single lead technique offers the advantage of simplicity of use without sacrifice of accuracy Its use can facilitate clinical studies of myocardial ischemic injury and its modification.

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Evaluation of outpatient arrhythmias utilizing transtelephonic monitoring

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Cardiac arrhythmias occurring in an outpatient setting form the basis of complaints ranging from minor palpitations to syncope. Certain rhythm disorders—for example paroxysmal atrial tachycardia—are believed to have distinctive clinical profiles which allow their recognition The purpose of this report is to evaluate the accuracy with which a group of physicians made the correct diagnosis based on history and physical examination.

The problems inherent in the clinical diagnosis of rhythm disturbances make electrocardiographic confirmation essential. This confirmation is often complicated by the transient nature of the problem. Although ambulatory monitoring with Holter electrocardiography has been used with some success, this technique is cumbersome and problems remain in reduction and reporting of these data. More importantly unless the arrhythmia appears during the recording period, it cannot be documented. Transtelephonic monitoring may be useful in this regard because the equipment is less cumbersome and the monitoring period may be extended indefinitely This report evaluates the use of this technique in the analysis of outpatient rhythm disturbances.

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*The views expressed herein are those of the authors and do not necessarily reflect the views of the U S Navy or the Department of Defense.

Materials and methods

Sixty-seven consecutive patients referred for analysis of symptomatic rhythm disturbances between 1977 and and 1978 were studied. Those patients with either previously diagnosed arrhythmias or pacemakers were excluded. After an initial evaluation which included a history physical examination, 12-lead electrocardiogram, and chest x ray the physician was required to select a single clinical diagnosis as to the exact nature of the arrhythmia (Table I). The patients were then referred for monitoring before any antiarrhythmic treatment was begun.

Each patient was given a transtelephonic monitoring system utilizing electrodes to be placed in each axilla. The patients were instructed to transmit an electrocardiogram during their typical symptoms. Patients who returned the system having failed to provide a transmission were interviewed to determine the reason for failure. Thirty five patients were also given a 12 hour Holter monitor using a modified V electrode which as then analyzed using a single channel scanner

Results

Sixty-seven patients were evaluated. They ranged in age from 26 to 81 years, with a mean age of 52 years. Forty-six were females and 21 were males. The presenting symptom was palpitation in 55 irregular heartbeat in eight, or near syncope in four Fifty two patients had no known cardiac disease. There were seven patients with coronary artery disease, five with mitral valve prolapse, one

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Table I Arrhythmia diagnosis in 36 patients (by clinical evaluation and by electrocardiographic monitoring)

Clinical di gnosis (N = 36)		*Diagnosis by transtelephonic monitoring (N = 32)*	*Diagnosis by Holter (N = 4)*	*Diagnosis by Holter & transtelephonic monitor (N = 3)*
N rmal	2	9	—	—
Paro ysmal trial tachycardia	16	3	—	1
Premature contractions	12	5	3	1
Atrial fibrillation	3	1	—	—
Atrial flutter	—	2	—	—
Ventricular tachycardia	1	—	—	—
Sinus tachycardia	2	12	—	1
Junctional Wenckebach	—	—	1	—
AV bl ck	—	—	—	—
Junctio al tachycardia	—	—	—	—
Sinus bradycardia	—	—	—	—

Table II Reasons for failure to provide a telephonic ECG transmission

	(n = 25)
No subsequent symptoms	12
Symptoms too brief	6
Patient non-compliance	2
Patient embarrassment	2
Patient' lack of understanding	1
System failure	1
Sudden death	1

Wolff Parkinson White syndrome one with a bicuspid aortic valve, and one patient with rheumatic heart disease.

The most common clinical diagnosis was paroxysmal atrial tachycardia (see Table I) In 36 patients an electrocardiogram was obtained by monitoring during symptoms. The clinical diagnosis in this group was substantiated in only 12 patients (33 per cent) Eight patients had premature contractions, one patient had sinus tachycardia, and three patients had paroxysmal atrial tachycardia (see Table I)

Thirty two patients (48 per cent) provided transtelephonic transmission at the time of a typical episode (See Table I) Thirty six patients were given a Holter monitor Of these nly se en had their typical symptoms during the 12 h ur recording (see Table I) Thirt fi patients (f2 per cent) returned their transtel ph nic monitoring device without having pr vided transm ssi n Twenty five were interviewed t t rmine th reason for this failure (see Table II). Twelve of these patients had had no further symptoms while in six the symptoms were too brief to record. In the remaining patients, two found the system embarrassing, one had a lead system failure, one failed to understand the system, and one died suddenly This latter patient was a 72 year-old male with coronary artery disease and palpitations who had not manifested arrhythmia during a resting electrocardiogram. Two patients failed to transmit even though they had had symptoms and understood the mechanism.

Discussion

The clinical diagnosis of a rhythm disturbance is based on several factors including the situation in which it occurs and specific features of the symptom including onset, offset, regularity duration and associated symptoms. Comparing the clinical diagnosis obtained utilizing these parameters with electrocardiographic documentation of the symptomatic episodes revealed that the clinical diagnosis was substantiated in only 33 per cent of the patients. Because management of rhythm disturbances depends on exact definition, electrocardiographic confirmation is necessary.

Several methods of confirmation have been used including Holter monitoring, treadmill exercise testing, and more recently transtelephonic transmission.[5-7] Holter monitoring is costly and data acquisition may be difficult. In addition the symptomatic episode may not occur during the recording period. Only 20 per cent of

our patients given Holter monitors had episodes during the recording. Treadmill exercise testing is also costly requires considerable equipment and symptomatic arrhythmias may occur only at rest. The transtelephonic monitoring system has the advantage of being inexpensive and can be provided for extended periods to permit transmission during symptomatic episodes. Thirty two of the patients studied provided a transmission during a symptomatic episode. The transmission established the diagnosis in 23 of these patients. The remaining nine had no rhythm abnormality during the transmission, even though they were symptomatic at that time.

Thirty five patients failed to provide a transmission for analysis. Follow-up interviews were obtained in 25 of these patients. Forty-eight per cent had had no further symptoms. This may in part be the result of a placebo response to the evaluation and physician reassurance. Six (24 per cent) of the patients failed to transmit because the symptom duration was too brief. Only 8 per cent found the system embarrassing to use. System failure and lack of patient compliance or understanding were infrequent causes of failure to provide a transmission.

Summary

This study demonstrates the inaccuracy of the presumptive clinical diagnosis of cardiac arrhythmia. Not only are physicians often wrong in establishing diagnoses on clinical grounds, in addition, a significant number of patients have symptoms which have been attributed to a cardiac basis when in fact, no rhythm abnormality exists. For this reason, electrocardiographic documentation is essential. This study defines the usefulness of transtelephonic monitoring in evaluating cardiac rhythm during a symptomatic episode suggestive of arrhythmia. It also defines the limitations of transtelephonic monitoring in patients whose symptoms are too brief or who would find the system awkward to use.

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Case reports

Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy

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Left ventricular dilatation has been found during postmortem examination in one patient who was known to have hypertrophic obstructive cardiomyopathy during life.

The progression to left ventricular dilatation, however has not been documented with clinical methods in patients with symptomatic hypertrophic obstructive cardiomyopathy developing congestive heart failure.

This paper reports on two patients with symptomatic hypertrophic obstructive cardiomyopathy who presented with congestive heart failure and a dilated left ventricle.

Case histories

Case 1 A 69-year-old woman underwent myotomy-myectomy in 1973 for symptomatic hypertrophic obstructive cardiomyopathy The histologic examination of the surgical specimen demonstrated characteristic abnormalities as found in hypertrophic cardiomyopathy

Despite improvement of her symptoms, beta-blocking medication was continued.

Echocardiographic examination in 1974 showed asymmetric septal hypertrophy (ASH) with ratio between interventricular septal thickness (IVS) to that of the left ventricular posterior wall (LVPW) of 2.0. Left ventricular (LV) size was normal and no signs of outflow obstruction were present. The left atrial (LA) cavity was slightly enlarged (Fig. 1) In December 1975, she was hospitalized because of severe congestive heart failure. The echocardiogram showed dramatic changes. Disproportionate thickening was now only seen in the upper part of the septum close to the aorta.

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Table I Pertinent echocardiographic data of the two patients with hypertrophic cardiomyopathy during congestive heart failure (A) and after medical treatment (B)

	Case 1		*Case 2*	
	A	*B*	*A*	*B*
LV dimension				
ED	90	60	70	64
ES	75	45	43	44
LA/Ao ratio	>1.5	1.4	1.9	1.7

Ao = aortic root; ED and ES = end-diastolic and end-systolic left ventricular internal dimensions in millimeters; LA, left atrium; LV, left ventricle.

In its midportion, the LV was extremely dilated (90 mm; upper limit of normal 56 mm.). LA size had increased and there was pericardial effusion. (see Fig. 2 and Table I) At cardiac catheterization, no pressure gradient across the LV outflow tract was measured and the dilated LV was confirmed by angiocardiography The coronary arteries were found to be normal. Beta-blocking therapy was discontinued and digitalis and diuretics were prescribed, resulting in clinical improvement. Follow-up echocardiographic studies over a period of [illegible] months showed decrease of the LV dimension up to 60 mm (Fig. 3).

Case 2. A 53-year-old man was operated upon for symptomatic hypertrophic obstructive cardiomyopathy in 1972 The preoperative hemodynamic study has revealed resting LV outflow gradient of 60 mm. Hg. The histologic examination of the excised septal muscle showed abnormalities typical for hypertrophic cardiomyopathy His symptoms improved subsequently and no medical treatment was felt necessary. The follow-up controls during three years occurred at another hospital. In January 1976, he was referred to our unit because of severe congestive heart failure. His echocardiogram made at admission showed LV dilatation (end-diastolic dimension 70 mm.) The LA was also dilated (ratio LA/Ao: 1.9, normal

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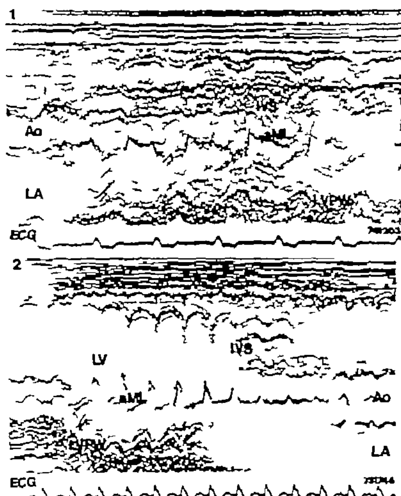


Fig. 1. Echocardiogram of case 1 in 1974. The interventricular septum (*IVS*) is thickened compared to the left ventricular posterior wall (*LVPW*). The left atrium (*LA*) is enlarged. (Ratio of LA to Aortic Root (*Ao*) is 1.4, normal value ≤ 1.2). Left ventricular (LV) size is normal (52 mm.).

Fig. 2. Echocardiogram of Case 1 during period of congestive heart failure in 1978. The interventricular septum (*IVS*) is thickened at the level just beneath the aortic valve, but thereafter significant thinning of the IVS is observed. Left ventricular posterior wall (*LVPW*) thickness is normal. Left ventricular sizes are enlarged to 60 mm. and 73 mm. in end-diastole and end-systole, respectively. Left atrial posterior wall is not registered on this tracing. Pericardial effusion is noted.

value ≤ 1.2). Remnants of septal hypertrophy were seen on the echocardiogram and were confined to the region just beneath the aortic valve (Fig. 4). Below that level, the septum was thin, possibly as a result of previous surgery and was akinetic.

Despite left ventricular failure, the left ventricular posterior wall still had an increased amplitude of motion. The patient was treated with digoxin and diuretics and the symptoms improved. The echocardiogram made 3 months later showed an LV end-diastolic diameter of 64 mm., while there was no apparent change in LA size (Table I).

Discussion

Left ventricular dilatation has been documented in one of 32 hearts from patients with previously known hypertrophic obstructive cardiomyopathy during necropsy examinations.

Frank and Braunwald[8] concluded from their analysis of 126 patients with hypertrophic cardiomyopathy that in this progressive disease with a variable clinical course, congestive heart failure was a rare complication. Only 20 patients in their series had cardiac enlargement on their routine chest film and only one was found with clinical signs of congestive heart failure. Adelman and colleagues[3] in a series of 60 patients, reported 7 per cent incidence of congestive heart failure. No data on their cardiac size was included. Shah and

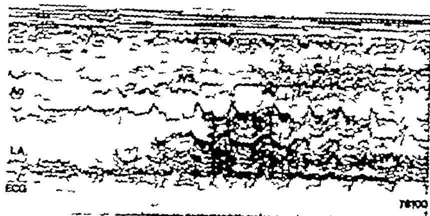


Fig 3 Echocardiogram of Case 1 in 1978. Significant changes occurred compared to *Fig. 2.* Left ventricular (LV) size has changed to 60 mm and 45 mm at *end-diastole* and *end-systole*, respectively. Left atrial size has significantly changed. (Ratio of LA to Aortic Root is 1.4 normal value ≤ 1.2).



Fig 4 Echocardiogram of Case 2 during period of congestive heart failure in 1978. Septal hypertrophy could only be seen just beneath the aortic valve, below that level the interventricular septum *(IVS)* is thin and akinetic. Left ventricular posterior wall *(LVPW)* has normal thickness and shows increased amplitude of motion. Left ventricular (LV) size is enlarged to 63 mm at end-diastole. The left atrial *(LA)* cavity is enlarged. (LA to Aortic Root *(Ao)* ratio 1.4, normal value ≤ 1.2)

Sylvester during an echocardiographic follow up study of 42 months in a small series of patients with hypertrophic obstructive cardiomyopathy could not demonstrate significant changes in left ventricular size. Thus, it appears that the development of congestive heart failure with dilated ventricle is a rare complication indeed.

Over a 4 year period, we have echocardiographically documented hypertrophic cardiomyopathy in 50 patients. Of these, 25 had systolic anterior motion of the anterior mitral valve leaflet in a narrow outflow tract typical for dynamic outflow obstruction. Ten were operated upon and are now being followed regularly. Five developed clinical signs of congestive heart failure, of which two had a dilated left ventricle and are described here.

It is difficult to infer an etiological factor for progression to LV dilation in hypertrophic obstructive cardiomyopathy. It is true that both patients underwent myotomy-myectomy but surgery has now been performed in many patients and follow-up data over periods of up to 14 years have been reported. No patient with progression to LV dilatation has been documented so far. Beta blocking treatment could have been a causative factor in Case 1. However this seems unlikely since more cases should have been found over the last decade, since beta-blockade is a

common treatment. Nonetheless, it appears that progression to congestive heart failure with left ventricular dilatation does occur as a rare complication in the course of hypertrophic obstructive cardiomyopathy

Summary

Congestive heart failure with dilated left ventricle developed in two patients with symptomatic hypertrophic obstructive cardiomyopathy Both patients previously underwent cardiac surgery for relief of their outflow obstruction.

Alterations in structure and function of the left ventricle during their episode of cardiac failure and thereafter were documented by echocardiography The findings suggest that progression to left ventricular dilatation is a potential complication in patients with hypertrophic obstructive cardiomyopathy

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Pathophysiologic observations on premature opening of the aortic valve utilizing a technique for multiplane echocardiographic analysis

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Premature opening of the aortic valve in severe aortic insufficiency was first reported by Page and Layton. Two recent reports demonstrate the same phenomenon as a complication of bacterial endocarditis. Weaver and colleagues described premature opening of the aortic valve occurring with every beat in a young patient with a torn left coronary cusp. Tafik and Guiliani[3] described premature opening of the aortic valve during the prolonged diastolic pause following a ventricular premature contraction and demonstrated an increase in peripheral arterial pressure presumably related to the premature opening of the aortic valve. This report demonstrates premature opening of the aortic valve in two patients with subacute aortic insufficiency. In one patient the development of the phenomenon was documented within a five month interval.

The mechanism underlying the occurrence of premature opening of the aortic valve has been the subject of controversy. We utilized a simple technique to analyze the motions of cardiac structures in different M mode echocardiographic planes in conjunction with an assessment of the effect of arrhythmia to provide additional information as to the possible pathophysiologic mechanisms involved.

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Echocardiographic methods

Echocardiograms were recorded with an Ekoline 20A recorder interfaced with a Cambridge strip chart recorder. A 2.25 MHz 10 cm. focus ½ inch transducer was used for all recordings. Recordings were made through a standard portal with the patient in the supine position.

A simple multiplane analysis technique was used for visualizing the relative motions of cardiac structures in different echocardiographic planes. A standard sweep was made from the aortic root down through the mitral valve to the left ventricle at the level of the mitral substructure. The sweep was done slowly to increase the likelihood of obtaining views in different echocardiographic planes with identical ECG R-R intervals. Echocardiographic tracings with identical R-R intervals were selected at the levels of the aortic root, the mitral valve, and the mitral valve substructure. Simultaneous motions in these different planes were then compared using a caliper and a "T-square" to identify comparable timing intervals relative to the ECG R wave. Septal motion may differ at the mitral and mitral substructure levels.[4] Therefore, in comparing septal motion at the mitral valve level with aortic valve motion, we first carefully confirmed that the temporal contour of septal motion was similar at the mitral level to that at the mitral substructure level.

Echocardiographic findings

Case 1

October 1975. A 29-year-old white male was admitted to the Boston V. A. Hospital for treatment of acute rheumatic fever with aortic insufficiency. There were no cardiac symptoms

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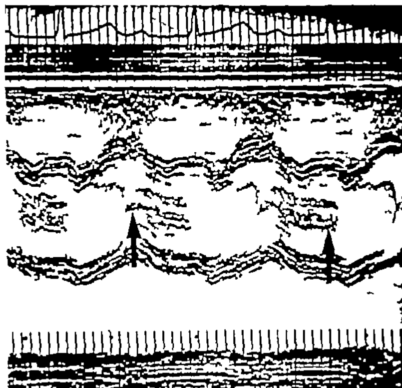


Fig. 1 Case 1, October, 1975. Aortic valve. *Arrows* show coapted leaflets in diastole. The leaflets remain coapted at the peak of the R wave of the ECG

Fig. 1 shows the aortic valve echocardiogram. Although the initial systolic opening of the valve leaflets was not well visualized, the leaflets remained coapted during diastole (*arrows*) at least until the mid-point of inscription of the R wave of the ECG. Premature opening did not occur. Fig. 2*A* shows septal motion at the mitral substructure level. The septum continued to move anteriorly throughout diastole after the transient posterior motion which normally follows mitral valve opening (*short arrows*). Echocardiographic dimensions are normal (Table I).

March, 1976. Five months later the patient developed overt congestive heart failure. Cardiac catheterization showed ++++ aortic insufficiency and left ventricular dilation with an ejection fraction of 61 per cent. An early diastolic shudder or recoil of the left ventricle was noted on the angiogram. Analysis of pressure tracings taken during pullback from the left ventricle to the central aorta showed that during post extrasystolic pauses left ventricular and central aortic diastolic pressures equilibrated approximately 160 msec. before the onset of the next P wave.

Echocardiographic recordings obtained after catheterization demonstrated dilatation of the left atrium and dilatation and decreased fractional shortening of the left ventricle (Table I). Septal motion at the mitral substructure level is demonstrated in Fig. 2*B*. Anterior septal movement was now interrupted in early diastole by a second transient posterior motion (*long arrows*), which occurred after the normal posterior motion associated with closure of the mitral valve after its initial rapid opening (*short arrows*). Multiplane analysis at the levels of the mitral and aortic valves for a period of equal R-R intervals is illustrated in Fig. 3. The second transient posterior septal motion, premature closure of the mitral valve, and premature opening of the aortic valve were all visualized. These three abnormalities, which were not present on the previous echocardiogram, all occurred at the same time and were simultaneous with the downslope of the P wave of the ECG.

Fig. 4 shows the critical effect of cardiac cycle length on premature opening of the aortic valve. In normal sinus beats 1 and 2, the aortic valve opened approximately 420 msec. after the onset of the R wave of the preceding ECG complex, which corresponds to the beginning of the P wave of the next ECG complex. Beat 3 is a premature ventricular contraction (PVC) which occurred approximately 400 msec. after the preceding R wave. Diastole was thereby shortened and premature opening of the aortic valve did not occur. The fourth beat occurred after a compensatory pause. The aortic valve opened during diastole approximately 420 msec. after the onset of the R wave of the preceding PVC and well before the inscription of the P wave of the next ECG complex. The valve remained open for a longer period during diastole and did not open further after the subsequent P wave. Beat 5 represents a return to the basic cycle length, and the valve again opened 420 msec. after the R wave of beat 4.

Case 2.

January, 1977. A 55-year-old black male was admitted to the Boston V. A. Hospital for evaluation of a new murmur of aortic insufficiency of unknown etiology. Cardiac catheterization revealed +++ aortic insufficiency. The left ventricle was not dilated, the ejection fraction was [illegible] per cent, and the

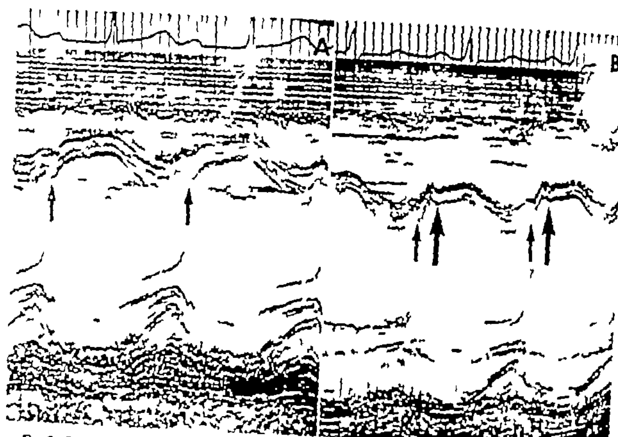


Fig. 2 *Panel A* Case 1 October 1975. Left ventricle at the level of the mitral valve substructure. *Panel B*, Same view in March, 1976. *Short arrows* indicate transient posterior septal motion which may be seen normally shortly after the B point of the mitral valve echocardiogram. *Long arrows* show the new posterior septal motion appearing in March, 1976 (Standardization is different in 2A and 2B).

cardiac index was normal. The left ventricular pressure was 120/25 mm Hg with an ... of 19 mm Hg.

April 1977 Over the next three months he developed dyspnea on exertion and increasing left ventricular hypertrophy with strain on ECG. He underwent aortic valve replacement.

Multiplane analysis showed that the premature opening coincided with the A point on the mitral valve echocardiogram (Fig). Fig 6 shows the aortic valve. Beats 1, 2, and 4 were normal sinus beats and beat 3 was a PVC. Premature opening of the aortic valve occurred before the first, second, and fourth beats, after completion of the P wave. The aortic valve did not open prematurely during the PVC. In contrast to Case 1, the prematurity was not increased when diastole was lengthened in the next beat, but maintained fixed relationship to the P wave.

Septal motion in this patient was normal, and fluttering of the anterior mitral leaflet was present. Septal and left ventricular posterior wall thicknesses were 1.3 cm (normal 0.9 to 1.1 cm.), demonstrating left ventricular hypertrophy. Left ventricular dimensions are otherwise normal.

Discussion

Premature opening of the aortic valve has been reported by several authors. The pathophysiologic mechanisms involved in its occurrence have been the subject of controversy.[5] We have had the opportunity to observe and correlate changes in clinical condition, multiplane analysis, and effects of arrhythmias on prematurity of opening to make certain inferences regarding the possible pathophysiologic mechanisms involved.

In Case 1 the premature opening of the aortic valve occurred at a fixed interval after the preceding R wave (Fig. 4) or after a specific critical period of ventricular filling. Moreover the lo... the diastole, the more premature the ope... presumably because critical ventricular filli... reached earlier in the diastolic cycle. The deve... ment of a new transient early diastolic poste... septal motion (Figs. 2 and 3) recorded echocar... graphically may correspond to the early diasto... shudder or recoil noted on the left ventricu... angiogram. Both findings suggest that there w... recoil of the elastic ventricular walls which gen... ated a rise in left ventricular pressure sufficient

Table I Echocardiographic dimensions (Case 1)

	October 1975	*March, 1976*
Aortic root, cm./M.	1.6	1.7
Left atrium, cm./M.	1.5	1.9
LV EDD cm.	5.6	6.3
LV ESD cm.	3.4	4.2
Fractional shortening, %	39.3	33.3
V_{cf} circ./sec.	1.51	1.10

LV EDD = left ventricular end-diastolic dimension; LV ESD = left ventricular end-systolic dimension; V_{cf} = velocity of circumferential fiber shortening.

open the aortic valve in diastole and to close the mitral valve prematurely. The synchrony of the new septal motion, premature opening of the aortic valve, and premature closure of the mitral valve (Fig. 3) support this hypothesis. This form of premature opening cannot be explained by atrial contraction, as has been suggested by Weaver and associates, since premature opening clearly preceded atrial electrical activation (Fig. 4). The primary pathophysiologic change that appeared to occur in this diastolic duration dependent form of premature opening of the aortic valve was a predominant dilatation of the ventricle in response to the volume overload, with little evidence for significant hypertrophy of muscle. The clinical correlate was the development of congestive failure and generalized cardiac dilatation on chest x ray.

A septal motion similar to that described above is occasionally seen in the echocardiogram of apparently normal patients at the level of the mitral valve. It occurs at the time of the F point and appears to be associated with, but not required for a subsequent anterior bulge of the anterior mitral leaflet during the F to A portion of the mitral echocardiogram (personal observation). It is much less prominent, however in normals. The frequency with which this motion can be visualized normally at the level of the mitral substructure is unknown.

In Patient 2 a different relationship was present. The time of premature opening was uninfluenced by the duration of diastole but did bear a fixed relationship to the end of the P wave of the ECG (Fig. 6). Multiplane analysis showed that the premature opening coincided with the A point of the mitral valve echocardiogram (Fig. 5). Septal motion was normal. The left ventricle was

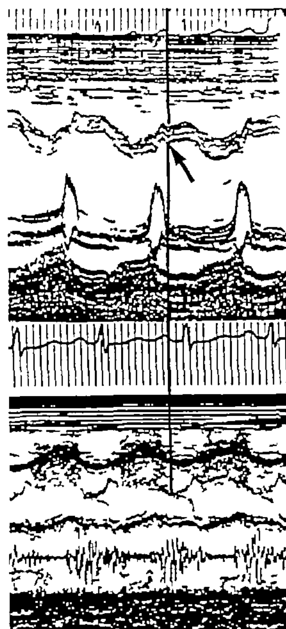


Fig. 3 Case 1, March, 1976. Multiplane analysis technique with identical R R intervals in the mitral valve *(upper panel)* and aortic valve planes *(lower panel). The continuous vertical line* demonstrates the synchronous occurrence of the transient posterior septal motion *(arrow)*, premature mitral valve closure, and premature opening of the aortic valve.

thickened without chamber dilatation. The a wave measured 19 mm. Hg at catheterization, suggesting relatively low compliance of the ventricle. In this patient, the force of atrial contraction against a hypertrophied ventricle evidently was of sufficient magnitude to open the

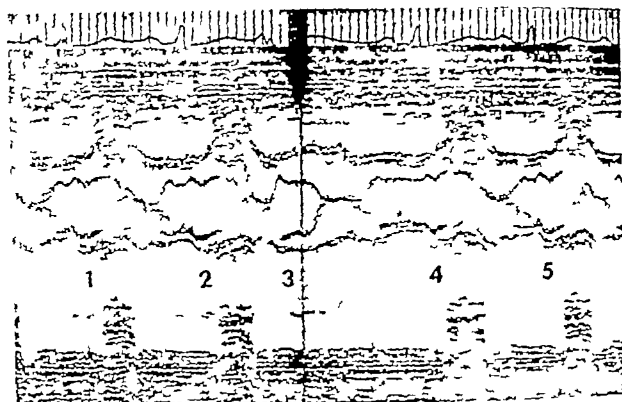


Fig. 4 Case 1, March, 19 &. Aortic valve. Premature opening of the aortic valve is accentuated in beat 4 when diastole is prolonged by the compensatory pause following the PVC.

aortic valve in diastole. The clinical correlate was the development of minimal congestive symptoms and of left ventricular prominence but minimal cardiac enlargement on chest x ray

It appears therefore, that there are at least two mechanisms for the phenomenon of premature opening of the aortic valve. In Patinet 1 the prematurity depended on the duration of diastole and was accompanied by a transient reverse movement of the interventricular septum. It occurred in the setting of marked ventricular dilatation. We propose that this form of premature opening of the aortic valve is due to the elastic recoil of the left ventricle from rapid early diastolic distention. In Patient 2, the premature opening coincided with atrial contraction and was independent of the duration of diastole. It occurred in the presence of left ventricular hypertrophy without dilatation. We propose that the mechanism in this form is forceful atrial ejection into a poorly compliant left ventricle The first form may be more dramatic echocardiographically as the aortic valve generally opens earlier in diastole than in the latter form. Whether each form is specific for the particular ventricular pathophysiologic response to aortic insufficiency, and whether a hypertrophied ventricle that subsequently dilates will convert from one mechanism to the other will require further investigation.

The previously reported cases of premature opening of the aortic valve were in patients with acute severe aortic insufficiency Our case material documents the same phenomenon in subacute aortic insufficiency Analysis of the acute insufficiency patients, in the light of our findings, leads us to conclude that they would fall into our diastolic duration-dependent subgroup. Wen[illegible] and associates'[7] case shows the same premature closure of the mitral valve and opening of the aortic valve before atrial activation and therefore contraction has occurred. The scale of reproduction makes comparable analysis difficult but suggests a similar septal recoil pattern in their Fig. 2. The occurrence of premature ventricular contractions in our comparable Case 1 (Fig. 4) shows that the valve opens well before atrial activation and that further opening occurs only after ventricular activation. This finding contradicts the hypothesis that atrial contraction plays



Fig. 5. Case 2, April, 1977 Multiplane analysis technique with identical R-R intervals in the mitral valve *(upper panel)* and aortic valve planes *(lower panel). The continuous vertical line* demonstrates the synchronous occurrence of atrial contraction (mitral valve A point) and premature opening of the aortic valve.

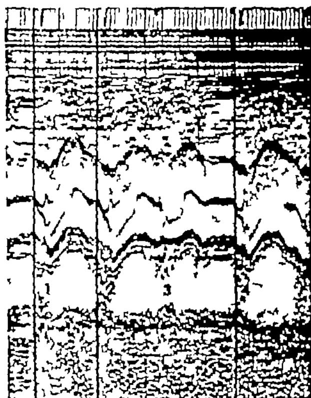


Fig. 6. Case 2, April, 1977 Aortic valve. *The vertical lines* identify the end of the P waves. Premature opening of the aortic valve occurs after atrial activation. Beat 3 is a PVC and premature opening of the aortic valve is absent. There is no increase in premature opening of the aortic valve in beat 4 despite prolongation of diastole by the compensatory pause.

a role in the diastole duration-dependent subgroup as has been previously suggested. Tajik and colleagues' case shows the phenomenon only in the prolonged diastole following a ventricular premature contraction and therefore is clearly diastolic duration-dependent. Our Case 2 therefore defines a different pathophysiologic subgroup which, in contrast to the diastolic duration dependent subgroup, *requires* atrial contraction against a hypertrophied ventricle to open the aortic valve prematurely

The multiplane analysis technique was useful in this investigation. The validity of this procedure depends on the assumption that hemodynamics remain constant between the observations at the different echocardiographic planes and that the effects of slight variations in the duration of the immediately preceding beats are insignificant. The possibility of hemodynamic changes should be minimized by obtaining the records for study within a period of several minutes. Correlation of ventricular wall, mitral valve, aortic valve, and left atrial motion is possible with this technique using a single echocardiographic recorder One obvious difficulty is the need to record fortuitously identical R R intervals while moving

the echo beam to different structures and planes. The occurrence of irregularities of rhythm and their effects on echocardiographic phenomena also provides additional unique information.

Summary

The use of a simple technique for multiplane echocardiographic analysis and study of the effect of arrhythmia enabled us to investigate the mechanism of premature opening of the aortic valve in two patients with subacute aortic insufficiency. In one patient, premature opening evolved with the development of left ventricular dilatation and failure. In this case the prematurity of opening in each beat was related to diastolic filling time and was accompanied by septal recoil and by premature closure of the mitral valve. We classified this as the diastolic duration-dependent subgroup. In the second patient, who had a hypertrophied, non-dilated left ventricle, premature opening depended on atrial contraction and was independent of diastolic filling time. This case defined an atrial contraction-dependent subgroup. In the light of these findings we analyzed previously reported cases in patients with acute severe aortic insufficiency. These patients appear to fall into the diastolic duration-dependent subgroup.

We wish to acknowledge the technical assistance of A. Johnson and Henry Johnston in obtaining the echocardiograms. Thanks also to Brad Milne of the Medical Illustration Department, and to Laurie Siegel, Geraldine Stockett, and Norma Spearin for typing of the manuscript.

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Clinical pathologic conference

Rupture of the ventricular septum as a complication of myocardial infarction

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CLINICAL SUMMARY This 67 year-old man was well until 3 weeks prior to admission when he experienced chest pain and shortness of breath. Nine days prior to admission, after an episode of chest pain that lasted an hour and a half the patient reported to a community hospital for evaluation. An electrocardiogram was interpreted as normal (Fig. 1) The patient returned home and went about his daily activities which included yard work and lifting heavy objects. Three days prior to admission, the patient experienced severe shortness of breath and malaise. This increased until the day of admission when he again went to the community hospital. At this time a new systolic murmur was heard. The electrocardiogram was unchanged and was now interpreted as compatible with an acute anteroseptal myocardial infarction. The patient was transferred to Walter Reed Army Medical Center for evaluation. He denied any cardiac awareness, palpitations, paroxysmal nocturnal dyspnea, orthopnea, or edema. He had no fever or chills. The patient had adult onset diabetes mellitus, controlled with diet, and a vague history of hypertension which was never treated. There was no family history of heart disease. The patient denied having rheumatic or scarlet fever gout, or hyperlipoproteinemia. He was taking no medications and was a nonsmoker

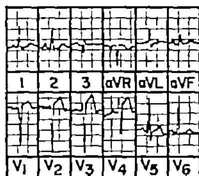


Fig 1 Electrocardiogram taken nine days prior to admission.

On physical examination the patient was in moderate respiratory distress, although alert and oriented. The pulse was regular and 104 per minute; respirations were 24 per minute and labored, and the blood pressure was 110/70 mm. Hg. He was afebrile. There was no jugular venous distension. The carotid upstroke was normal. On auscultation bilateral basilar râles were heard as high as the scapulae. There was a precordial systolic thrill felt best at the left lower sternal border The patient had a Grade IV/VI holosystolic murmur heard best at the lower left sternal border and radiating over the entire precordium. In addition, there was a Grade I II early diastolic rumble heard best at the apex. S_1 and S_2 were normal. The liver span at the right mid-clavicular line was 10 cm. The liver was tender and the left lobe was prominent. The rest of the physical examination was normal.

The patient had a mild leukocytosis with a shift to the left. Urinalysis was normal. The blood

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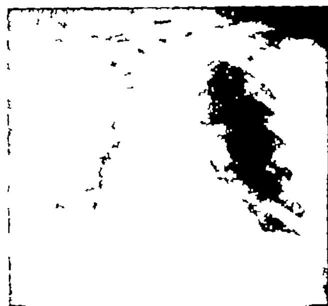


Fig 2 A portable anteroposterior chest x-ray taken on admission.

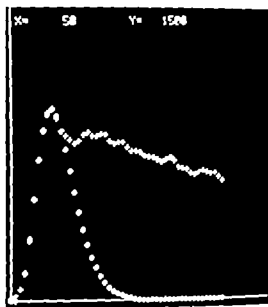


Fig. 3. Pulmonary time–activity histogram (+) and gam[ma] function fit (○). The marked difference between the pul[mo]nary time–activity and gamma function fit curves that oc[cur] shortly after peak suggests the presence of large left-to-r[ight] shunt. The calculated ratio of pulmonary to systemic bl[ood] flow is greater than 3.

glucose was 437 mg per cent. The blood urea nitrogen was 1.9 mg per cent. The serum electrolytes were all abnormal, sodium 129 mEq./L., potassium 6.0 mEq./L., chloride 97 mEq./L., and CO_2 17 mEq./L. Arterial blood gases were drawn while the patient was breathing room air The oxygen partial pressure (PO) was 80 mm. Hg the carbon dioxide partial pressure (PCO) was 18 mm. Hg, and the pH was 7.54. On admission the serum glutamic oxaloacetic transaminase (SGOT) was 802 units, lactic dehydrogenase (LDH) 2,600 units, creatine phosphokinase (CPK) activity 63 units. All LDH isoenzyme fractions were elevated, although fractions one and two (cardiac fractions) were markedly increased. CPK isoenzymes were all within the M band. Thyroid function tests were normal.

Clinical discussion

DR. JULIUS L. BEDYNEK. First I should like to ask Dr Anderson to interpret the electrocardiograms and chest x rays.

DR. WARREN T ANDERSON On the initial tracing 9 days prior to admission (Fig. 1) there was a sinus tachycardia of 110 beats per minute. The slow R wave progression through V and ST segment elevation in V through V suggest an acute anteroseptal myocardial infarction. The tracing on admission and subsequent tracings demonstrated further evolution of an anteroseptal myocardial infarction. The chest x ray on admission (Fig. 2), although a portable AP fil[m] demonstrated mild cardiomegaly and promine[nt] pulmonary vascularity On multiple repeat fil[ms] throughout the hospital course there was progre[s]sive cardiomegaly and marked increased pulmo[nary] congestion.

DR. BEDYNEK In summary this was a 67 yea[r] old man who suffered an acute anterior myoca[r]dial infarction. Six days later he suddenly deve[l]oped signs and symptoms of congestive hea[rt] failure with pulmonary congestion. Subsequent[ly] a loud systolic precordial murmur and a thri[ll] both maximal at the lower left sternal borde[r] were noted.

This case poses the problem of the differenti[al] diagnosis of systolic murmurs associated with t[he] sudden clinical deterioration of the patient wi[th] an acute myocardial infarction. The determina[]tion of the cause of the systolic murmur is [of] practical importance in predicting the course a[nd] determining the management of these patient[s]. The most important entities in this differentia[l] diagnosis are rupture of the ventricular septu[m] and rupture of a papillary muscle with acu[te] mitral regurgitation. However papillary musc[le] dysfunction and acute dilatation of the le[ft] ventricle may also be associated with the sudde[n]

Table I Differential diagnosis of systolic murmurs appearing during the course of myocardial infarction

	Septal rupture	*Papillary muscle rupture*	*Papillary muscle dysfunction without rupture*	*Acute left ventricular dilatation*
Incidence	Up to 1% of transmural infarction	Up to 1% of all cases	More frequent (up to 57% of infarctions) & more transient	Not clear, but when present probably clears w/treatment of failure
Location of infarction	Usually anteroseptal or posteroseptal	Usually inferior	← Ischemia and/or infarction → ST T changes antero-lateral or inferior	Location not critical
Appearance	4 to 7 days post-infarction	Later than septal rupture/even wks. to mos.	At time of chest pain (ischemia) & may persist	At time of dilatation
Murmur	Left sternal border Almost always present and loud (G III & IV)	Apex w/radiation to axilla or base (G II or less). Absent in 40%	II/VI or less at apex (Gr I to II in 2/3)	Apex and soft
Thrill	Left sternal border Present in 50% of cases	Apex and unusually present	Very unusual	Unusual
Conduction defect	In up to 40%	Unusual	Unusual	Unusual
Heart failure	Progressive w/left & right-sided features	Acute onset of left sided failure & acute pulmonary edema	Not prominent	Common
Prognosis	Poor with or without surgery	Guarded with or without surgery	Good short-term, poor long-term due to new infarction	Not clear

appearance of a loud systolic murmur and dramatic deterioration of the patient. The important criteria in the differential diagnosis of these systolic murmurs are summarized in Table I.

Our patient had many of the features of acute rupture of the ventricular septum. This unusual complication of myocardial infarction occurs in up to one per cent of transmural infarctions involving the ventricular septum. The murmur and thrill usually appear four to seven days after the infarct, as apparently was the case in our patient, and are usually maximal at the lower left sternal border a location consistent with the findings in congenital ventricular septal defects. I can recall, however two patients which were exceptions to this rule. In these two patients the murmur and thrill were most intense at the apex and in the axilla. In both patients a ventricular septal defect was proven by cardiac catheterization. I know of no good explanation for the paradoxical physical findings (murmur and thrill more intense at the apex than at the left sternal border) in either of these patients.

Since the His bundle and bundle branches may be involved in septal infarcts, a conduction defect is present in up to 40 per cent of the patients with ventricular septal rupture. This patient did not have a conduction defect. Usually there is a substantial left to-right intracardiac shunt across the defect and features of left and right heart failure are virtually constant in these patients. In my experience patients without prominent congestive heart failure have had small ventricular septal defects. These patients have a better overall prognosis, since successful surgical therapy largely depends on the ability of the patient to survive for four to six weeks after infarction, allowing time for the margins of the infarcted myocardium to heal sufficiently to support sutures.

Rupture of a papillary muscle is also frequently associated with dramatic clinical deterioration and the appearance of a loud systolic murmur. These patients usually have an infero-lateral myocardial infarct.[1] Papillary muscle rupture occurs in up to one per cent in all cases of myocardial infarct, usually later than ventricular septal rupture and occasionally several months

after the infarct. The murmur of mitral regurgitation may be absent in up to 40 per cent of these cases, and when present is usually loudest at the apex with radiation to the axilla or to the base of the heart. A murmur is more frequently detected with partial rupture of a papillary muscle. Radiation to the base implies rupture of the posterior medial papillary muscle and radiation to the apex rupture of the anterior papillary muscle. A thrill is uncommon but, if present, is frequently most intense at the apex Conduction defects are rare Heart failure is most often of acute onset with fulminant pulmonary edema. The prognosis is guarded and is often worse than that in ventricular septal rupture, except with partial rupture of a papillary muscle. Since survival is longer with partial rupture attempts at surgical repair are more frequently successful.

Papillary muscle dysfunction without papillary muscle rupture is also a frequent cause of a systolic murmur appearing during the course of myocardial infarction and has been reported in up to 57 per cent of all cases of infarction The murmur is usually pansystolic and apical in location and is most often softer than the murmur of septal rupture. It is Grade I to II/VI in two thirds, and Grades II to IV/VI in one third of the patients. The murmur is usually not associated with marked deterioration of the patient but may be associated with both radiographic and clinical findings of left ventricular failure. The murmur may be appreciated during chest pain connoting myocardial ischemia and may be accompanied by ST and T wave changes in the ECG Those ECG changes include mild to severe depression of the J junction with convex or concave upward deformity of the ST segment and frequently terminal inversion of the T wave or depression of the T U segment with U wave inversion in the middle and left precordial leads especially in anterolateral papillary muscle dysfunction. Papillary muscle dysfunction may be a manifestation of transient severe ischemia or may imply the infarction of a papillary muscle. Thrills, conduction defects, and severe heart failure are uncommon. The prognosis is good for short term survival. Long term prognosis, however is poor as those patients frequently have severe obstructive coronary disease

Acute left ventricular dilatation during the course of myocardial infarction may disrupt the configuration of the mitral valvular apparatus sufficiently to cause mitral insufficiency As papillary muscle dysfunction myocardial infarction is not necessary for the appearance of the murmur and it may occur with transient severe myocardial ischemia or ischemic myocardiopathy It is hypothesized that the mitral valve becomes incompetent because the bases of the papillary muscles are widely separated due to dilatation of the ventricular cavity and the chordae tendineae lie at an obtuse angle to the mitral leaflets. The result is incomplete closure of the mitral valve during ventricular systole. This explanation is currently preferred over the more classical one that the mitral valve ring is simply dilated. I am not aware, however that either hypothesis has been proven by objective investigations. Heart failure is common, but rarely of sudden onset. The clinical history and physical findings suggest either left ventricular dilatation or papillary muscle dysfunction as a cause of the murmur

This discussion would not be complete without mentioning three other possible causes of systolic murmurs, all unlikely in our patient, appearing following myocardial infarction. These are pericarditis, rupture of the ventricular free wall, and right ventricular infarction with tricuspid regurgitation. Pericardial friction rubs secondary to pericarditis are quite frequent during the course of acute myocardial infarction especially when listened for carefully It is entirely possible that a systolic friction rub could be confused with a systolic murmur and in the occasional instance where pericardial fluid is copious, deterioration due to pericardial tamponade might result after the appearance of such an auscultatory finding The careful search for a three-part friction rub would help eliminate this point of confusion.

Rupture of the ventricular free wall may be preceded by a transient systolic murmur This is soon followed by signs of cardiac tamponade. The systolic murmur has been attributed to actual systolic leakage of blood into the pericardial cavity Electromechanical dissociation is common and usually fatal within minutes in these patients. Those few patients who have survived with expeditious surgery have done so only because there was a high index of suspicion and because pericardiocentesis was carried out while the patient was in route to surgery I am not, however aware of any long term survivors.

Rupture of a tricuspid valve papillary muscl

producing a systolic murmur at the lower sternal border in the course of myocardial infarction has been reported. In this single reported case the heart failure was predominantly right-sided.

The two most likely diagnostic possibilities in our patient are ventricular septal rupture and papillary muscle rupture, and I will confine my further discussion to these two entities. The clinical course is, of course, of particular interest at this point. Dr Wheeler cared for this patient in the coronary care unit, and I will call on him now to discuss the clinical course.

DR. LEIGH WHEELER. The patient was admitted to the CCU where his deteriorating course was compatible with either ventricular septal perforation or acute mitral regurgitation secondary to a papillary muscle dysfunction. The patient was treated with digoxin, oxygen, and diuretic therapy. Because of the difficulty in identifying the cause of the systolic murmur the patient was taken to the cardiac catheterization laboratory on the third hospital day where a balloon tipped, flow directed catheter was introduced into the right heart. Each time the catheter tip was advanced to the right ventricle, it was rapidly ejected into the pulmonary artery and on four occasions the cardiac rhythm immediately deteriorated to ventricular fibrillation. The catheter was withdrawn, and the patient was successfully electrically defibrillated. Since a diagnosis was not established by catheterization, a radionuclide angiocardiogram was done by Dr Kaminski.

DR. ROBERT KAMINSKI The radionuclide angiocardiogram was done on the seventh hospital day A bolus of 15 mCi 99m Technetium pertechnetate was injected intravenously through a central venous pressure catheter and images of the anterior chest were immediately obtained by a gamma camera interfaced with a computer Data was collected at 0.5 second intervals for 1 minute and subsequently analyzed using the method for quantitation of left to-right shunts described by Askenazi and colleagues. The derived pulmonary time-activity histogram, and the gamma function fit are shown in Fig. 3. The gamma fit approximates the first passage of tracer through the lungs without recirculation, and the area under the curve is proportional to the pulmonary blood flow The difference between the fitted curve and the original data is due initially to recirculation secondary to the shunt, followed by recirculation of tracer that has passed through the systemic circulation. In normal individuals the pulmonary curve and gamma fit closely approximate each other until systemic recirculation occurs. In this case, however there is a very early deviation of data from the gamma fit suggesting a large left to-right shunt. The presence of a shunt was also confirmed visually by persistence of radioactivity over the lung fields and right heart chambers. The calculated ratio of pulmonary to systemic blood flow (Qp/Qs) was greater than 3. Published reports have shown close correlation between the nuclide angiocardiography in left to-right shunts with Qp/Qs ratio of 1.2 to 3.0. Shunts in which the ratio of pulmonary to systemic blood flow is greater than 3 will not escape detection, but frequently cannot be precisely quantitated by this method. Precise quantitation of shunts of this magnitude, however is probably not of clinical importance. This technique is non-invasive and requires a minimum of patient time in the nuclear medicine clinic. Thus, it is well suited for the critically ill individual in whom angiography may not be well tolerated.

DR. WHEELER. The patient s course in the coronary care unit was one of continued hyperglycemia managed with insulin, subcutaneous or intravenous, as appropriate. The patient maintained a persistent respiratory alkalosis which was managed with an O -CO delivery system. On this regimen, his arterial blood pH fell from 7 6 to 7 48. The patient developed severe azotemia probably secondary to poor cardiac output. Efforts were made to fluid re-expand the patient while carefully following his ability to oxygenate. Vasodilator ventricular unloading therapy (nitroglycerin paste) was begun on the eighth hospital day The patient remained relatively stable through the first 13 days of his hospitalization. It should be noted that throughout this period, the patient refused any type of surgical intervention on the basis of his religion. On the 14th hospital day the patient developed a purulent discharge from a central catheter site and *Staphylococcus aureus* was cultured from the blood as well as the wound. Intravenous penicillin therapy was initiated. Because of a change in mental status and a decrease in urine output, the patient was given low dose dopamine therapy on the 17th hospital day The patient responded and, by the 19th hospital day was awake and lucid. On the evening of the 19th hospital day the patient became

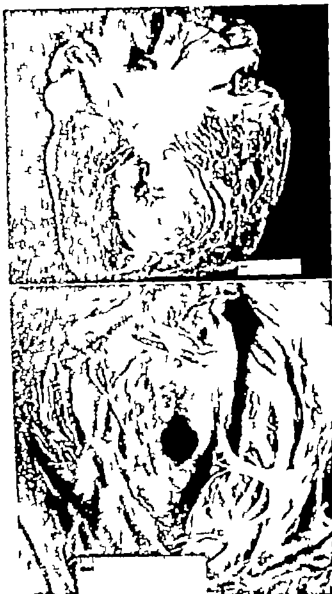


Fig 4 Ventricular septal defect, produced by rupture of the septal myocardium following a myocardial infarct. From the left side of the heart (*upper panel*) the defect is clearly seen in the mid-ventricular septum just beneath the anterior leaflet of the mitral valve The smooth margins of the defect seen from the right side of the heart (*lower panel*) suggest that the rupture of the ventricular septum occurred weeks before the patient demise

hypotensive. Nitroglycerin paste was discontinued and dopamine was increased slightly On the morning of the 20th hospital day his urine output decreased. He became hypothermic, developed a wide QRS and sinus brachycardia, and died.

DR. BEDYNEK Dr Wheeler has brought up the usual problem in such patients the differential between ventricular septal rupture and papillary muscle rupture. This differential is difficult on the clinical grounds, alone although our patient had findings pointing to the former An accurate diagnosis can obviously be made by taking the patient to the cardiac catheterization laboratory and doing both right and left-sided heart catheterization. A left ventriculogram in the steep left anterior oblique projection has its advocates since this will demonstrate a ventricular septal defect or mitral insufficiency This procedure has the added advantage of revealing a co-existent ventricular aneurysm, and elucidating the functional status of the remaining viable myocardium. Since the patient is presumed a candidate for reparative surgery at this point, coronary angiography is often considered necessary and can be done concurrently The disadvantages obviously include the poor tolerance of acutely ill patients to injections of fairly large volumes of contrast medium into the irritable left ventricle with the likelihood of ectopy acute worsening of failure due to the volume effect, and the possibility of dislodging mural thrombi with embolization to the systemic circulation.

An alternate approach now possible in most coronary and intensive care units does not require the transportation of the patient to the catheterization laboratory but can usually be done at the bedside with the anticipation of an accurate differential diagnosis at least between the two most likely possibilities—that is ventricular septal rupture and papillary muscle rupture. This is the technique of Swan and associates,[5] which is generally regarded as more convenient, more rapid, and safer than even conventional right sided catheterization. This technique was designed precisely for this purpose of differentiating ventricular septal from papillary muscle rupture. The diagnosis of ventricular septal rupture is suggested by a step-up of one volume per cent or greater of oxygen content in the blood of the right ventricle, compared to the right atrium.[6] The presence of "giant V waves" in the pulmonary wedge tracing without an oxygen step-up supports the diagnosis of acute mitral insufficiency from papillary muscle rupture. The obvious disadvantages are the inability of the technique to provide data on left ventricular function and anatomy and failure to visualize the coronary vessels. This procedure was attempted in our patient in the catheterization laboratory but was unsuccessful because of recurrent ventricular fibrillation, and the patient was returned to the

coronary care unit without definitive diagnosis.

Other reports have stressed the safety of this technique, but in our case the rapid whipping of the catheter from the right ventricle to the pulmonary outflow tract, presumably under the influence of an augmented right ventricular output, was enough to irritate the right ventricular endocardium and produce arrhythmia. Our experience is in keeping with a recent report of Kaplan and co-workers of serious complications of ventricular ectopy when a patient was studied in the cardiac catheterization laboratory following rupture of the ventricular septum.

The definitive diagnostic procedure carried out in this patient was a radionuclide angiocardiogram. This technique is simpler and less hazardous than other techniques. The time required to do this study is usually quite short, and the size of the left-to-right shunt in terms of a ratio of pulmonic to systemic flow can usually be accurately determined, an advantage of this technique over the transvenous placement of a platinum-tipped electrode in the right ventricle and inhalation of hydrogen gas. The disadvantage of the isotope technique is that it cannot accurately localize the shunt.

The presence, however of a murmur and thrill at the left sternal border in the presence of a documented intracardiac shunt, is presumptive evidence of a ventricular septal defect. In our patient the radionuclide angiocardiogram documented the presence of a large left-to-right shunt.

I should mention the recent application of echocardiography to the differential diagnosis in question. In patients with ventricular septal rupture the findings are not specific, and consist of dilatation of the right ventricle, normal septal motion, and occasionally slight increase in left atrial diameter. In one report there was an unusual pattern of mitral valve motion consisting of closure of the mitral valve after initial opening in early diastole followed by almost complete reopening of the valve.[12] The pattern suggested increased blood flow across the mitral valve. In contrast the echocardiographic findings in acute mitral insufficiency following rupture of the chordae tendineae include flail leaflets, abnormalities of coaptation, abnormal movements of the leaflets in diastole, and systolic fluttering of the leaflets.

Although I suspect the findings would be similar I do not know of a case report of the echocardiographic findings in rupture of a papillary muscle. Furthermore, I do not believe these findings can be regarded as specific enough for definitive diagnosis. A new technique, pulsed Doppler echocardiography which allows detection of direction, as well as location of tubulent blood flow has been applied to differentiation of ventricular septal defect from mitral regurgitation in children.[13] In 39 of 40 cases the findings with this technique agreed with the clinical or catheterization evidence. This technique may be applicable to the problem under discussion in the future.

Early definitive diagnosis is essential in these patients. Immediate surgery in spite of the fact that such surgery is less successful when done early in the course of either ventricular septal defect or papillary muscle rupture, offers the only hope of reducing mortality rate. There are reports of survival rates of up to 50 per cent with early surgery in either ventricular septal or papillary muscle rupture, even in patients with dramatic clinical deterioration. Without surgery the mortality rate in these patients is virtually 100 per cent. Unfortunately our patient refused surgery.

In summary my diagnosis is ventricular septal rupture with large left-to-right shunt across an acquired ventricular septal defect occurring following an acute anteroseptal myocardial infarction.

Autopsy findings

DR. JOHN J. FENOGLIO At autopsy the heart was enlarged and weighed 585 grams. The lumens of the coronary arteries were extensively compromised by atherosclerotic plaques with 80 per cent occlusion of the left anterior descending artery 70 per cent occlusion of the right coronary artery and near total occlusion of the posterior branch of the left circumflex artery. No thrombi were found, however in any of the coronary arteries.

On opening the heart, there was a large defect in the anterior mid ventricular septum measuring 1.5 to 2.0 cm. in diameter (Fig. 4). The edges of the defect were smooth and the defect was surrounded by a healing infarct which involved the entire ventricular septum but spared the anterior papillary muscle. Microscopically the area of the infarct consisted of proliferating fibrous tissue and abundant chronic inflammato-

ry cells, predominantly lymphocytes and histiocytes. Islands of necrotic hyalinized cardiac muscle were trapped within the fibrous tissue and surrounded by chronic inflammatory cells. There was no evidence of an acute infarct, as evidenced by infiltrates of polymorphonuclear cells, even in the areas of necrotic myocardium. Microscopically the infarct was three to six weeks of age. The margins of the ventricular septal defect consisted of proliferating fibrous tissue and the surface was covered by endocardial cells, suggesting that the [illegible]ntricular septum ruptured during the acute [illegible]ase of the myocardial infarct, within the first [illegible] [illegible]eks.

[illegible] small organizing mural thrombus was present in the right atrium. There was evidence of [illegible] acute and chronic passive congestion in [illegible] other [illegible]iscera especially in the lungs, liver an[illegible] [illegible]n

Diagnoses Coronary atherosclerosis, moderate to severe with three vessel involvement myocardial infarct, recent healing septal, with rupture of the ventricular septum.

DR. HUGH A McALLISTER Recently Vlodaver and Edwards reviewed their experience with 98 hearts with rupture of some portion of the left ventricle or ventricular septum as a complication of acute myocardial infarction Anteroseptal infarction was associated with ventricular septal rupture in 50 per cent of their cases inferior location of the infarct accounted for 28 per cent. Inferiolateral location of the underlying infarct was the most common situation in ruptured papillary muscle. In each of their cases involving rupture of the left ventricular free wall or of the ventricular septum, whether isolated or in association with rupture of another structure the infarct was transmural. In contrast, the infarct was subendocardial in slightly over 50 per cent of the patients with isolated rupture of a papillary muscle. As in other studies, rupture of the anterolateral papillary muscle was less common than rupture of the posteromedial papillary muscle.

Again similar to the observation of others, the time of rupture of the ventricular septum or of a papillary muscle after the onset of myocardial infarction was commonly within the first week, with the greatest concentration by the third day Death within one week was usual after rupture of the ventricular septum or with total rupture of a papillary muscle.

In the series by Vlodaver and Edwards, atrioventricular conduction disturbances were observed in 36 per cent of 17 cases with rupture of the ventricular septum James,[14] however reported the findings in five patients with acute posterior myocardial infarction by electrocardiographic definition who died following rupture of the ventricular septum These five patients developed varying degrees of atrioventricular block prior to rupture of the ventricular septum. In three of these five the time of septal rupture coincided with the resumption of conducted sinus rhythm. Multiple major coronary artery atheroma were present in all five of these hearts, and a recent thrombus was present in the right coronary artery in four of these five cases.

Multiple atheroma with significant luminal narrowing are usually present in each of the major coronary arteries in patients with rupture of the ventricular septum. The role of the thrombus remains controversial.

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Fundamentals of clinical cardiology

Bedside management of acute myocardial infarction

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[illegible] year about one million people in the United States suffer an attack of acute myocardial infarction. Between 50 to 60 per cent of [illegible] acute infarctions occur outside the hospital. More than 40 per cent die within the first two hours after the onset of symptoms. Prehospital care has been shown to be feasible and of great value. Emergency medical systems (mobile coronary care units) are now available in many cities. If such units are not available, the patient should be taken to a hospital as rapidly as possible. In view of the increased incidence of arrhythmias during the first few hours of an acute infarction, it has been suggested that prophylactic prehospital treatment with lidocaine or atropine be administered. Until further studies become available, we recommend the prehospital use of 300 mg. lidocaine intramuscularly if the heart rate is over 55 beats per minute, or atropine 0.6 mg. intravenously if the rate is below 55 beats per minute. However, a recent hospital study did not confirm this dose of lidocaine as effective in preventing primary ventricular fibrillation, possibly because the blood levels of the drug were inadequate. In addition, the mechanism of arrhythmias in the earliest phase of myocardial infarction may be different from that in later stages. Therefore, the variable results may be due to the different times from the onset of the infarction that lidocaine has been administered.

Many factors contribute to the delay in early hospitalization of these patients. The patients may not seek medical aid immediately. The family doctor may not be aware of the high risk of sudden and preventable death in an apparently mild attack, or may consider it to be an anginal attack. When the patient gets to the hospital, there should not be a delay in transfer from emergency room or admitting office to the coronary care unit. Treatment in coronary care units has been credited with saving up to one-third of the hospitalized patients who formerly would have died from acute myocardial infarctions.

All hospitals, regardless of size, should have coronary care units. Many small community hospitals cannot afford to set beds aside for this service or to provide trained staff. However, in a small hospital, a two bed unit can be set up next to the main general nursing station where both patients and monitor can be easily observed. In such a small hospital having few patients with coronary attacks, the unit might be called a cardiac intensive care unit rather than the standard coronary care unit and might also provide monitoring of patients who have not sustained acute myocardial infarction but have life-threatening arrhythmias or other cardiac complications. General duty nurses can be trained to recognize life-threatening arrhythmias and to begin cardiopulmonary resuscitation when cardiac arrest occurs. In this setting, a policy of giving priority to patients with coronary attacks and transferring other patients from the unit would be mandatory.

The nurses' responsibilities vary depending on the type of hospital and the availability of house staff or other physicians. Especially in hospitals without a house staff, in addition to using the defibrillator, they may be permitted to give intra-

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venous lidocaine, atropine, and other medications on their own initiative in situations defined in a unit protocol. Authorization for these procedures should be approved by the medical and nursing staff.

A team of physicians should be responsible for establishing and maintaining the unit policy. Successful operation of these units depends on the cooperation of all physicians who admit patients to them. These physicians must abide by the policies of the unit. It is our policy to admit to the unit all patients with suspected or known acute myocardial infarctions, regardless of the severity of the attack. After four days, patients are transferred elsewhere in the hospital if their condition is stable. In some hospitals monitoring is continued telemetrically after patients leave the unit.

Coronary patients may have psychologic stresses and go through many emotional phases. The physician and nurse therefore should discuss with the patient his condition, care, and future. Plans should be made for continued care once the patient leaves the unit.

General management

Pain. On arrival at the unit, an intravenous infusion should be started. The patients with acute myocardial infarctions should immediately receive opiates for relief of pain. Pain can cause coronary spasm and can stimulate excretion of catecholamines, which can produce an increase in heart rate, cardiac output, heart work, and arrhythmias. However, opiates may decrease alveolar ventilation with increased right-to-left shunting and decrease in arterial PO_2. Focal atelectasis and ventilation–perfusion abnormalities can occur because of the decrease in frequency and depths of respirations. Many different opiates can be used. The right coronary artery usually supplies the inferior and true posterior areas of the heart and in 90 per cent of cases the A-V node. If it is occluded, then these patients are prone to bradyarrhythmias, especially atrioventricular heart block. Therefore, we prefer that morphine, a vagomimetic agent, not be given to such patients with inferior or posterior infarctions since it may aggravate or even precipitate sinus bradycardia, slow junctional rhythms, and atrioventricular heart block. Meperidine (Demerol), although not as effective as morphine, is frequently used in a dosage schedule of 50 to 100 mg. every three to four hours. Pentazocine (Talwin) is not recommended, for it may elevate left ventricular filling pressure and raise systemic vascular resistance and as a result may augment myocardial oxygen requirements and thus exacerbate ventricular ischemia. It also has a direct negative inotropic effect. A mild sedative is often necessary. Diazepam (Valium) does not alter warfarin action. In addition it reduces left ventricular filling pressure and arterial pressure[7] and it reduces excretion of catecholamines. The former action exerts a beneficial action on depressed left ventricular function and the latter action may diminish the incidence of malignant arrhythmias and prevent existing myocardial injury from spreading. A recent study[8] emphasized the relation between stress, enhanced sympathetic activity, and ventricular arrhythmias. If hypotension is not present, we usually give 5 to 10 mg. diazepam orally three times per day. Flurazepam (Dalmane) may be used as a hypnotic.

Opiates and sedatives should be given cautiously to confused and restless patients suffering from cerebral dysfunction due to shock or heart failure.

Oxygen. Oxygen is recommended for all patients with acute myocardial infarctions. Hypoxemia may exist even in the uncomplicated cases because of ventilation–perfusion abnormalities. Madias and colleagues[10] showed that oxygen reduces ST segment evidence of myocardial ischemia. Forty per cent oxygen can safely be given to patients with myocardial infarction. One hundred per cent oxygen may be required for patients in pulmonary edema or cardiogenic shock.

Bed rest. In 1952 Levine and Lown demonstrated that a patient could be moved into an armchair during the initial stages of an acute myocardial infarction without deleterious effects. This was the first step toward shortening bed rest and the length of hospital stay. Recently a study showed that uncomplicated cases can be discharged one week after acute myocardial infarction. These patients at the six month follow-up had a low incidence of late serious complications which were no more than in the control group.

At present we allow the patient with an uncomplicated acute myocardial infarction to sit in a bedside chair by the third day. Also at this time

he may sit at the bedside for a few minutes, three to four times per day and flex and extend his feet and legs. A bedside commode is allowed immediately. The patient can sit up on his own and is not lifted onto the armchair or commode. Personal activities, such as feeding, washing, etc., are also done on his own. By the end of the first week we allow him to walk slowly to the bathroom and down to the nurses station. If no complications occur activity is gradually increased so that the patient is ambulating as much as desired prior to discharge at 2 weeks. Studies have shown that there are no special benefits to be gained by prolonged hospitalization beyond two weeks. In addition expenses are reduced and patients rest better at home in their customary surroundings.

These activities are modified if persistent chest pain, shock, severe heart failure, or major arrhythmias occur. Usually activities are begun after complications have been successfully treated.

Diet. We allow the patient to feed himself from the start. Clear liquids are given on the first day and full liquids on the second. After this, the diet depends on the lipid analysis, body weight, carbohydrate metabolism, and other factors. During the acute phase of an infarction, lipid values are altered, and measurements should be repeated during the convalescent period. One study indicated the drop in lipid levels occurred 36 hours after the onset of symptoms. In that study plasma lipid levels on the morning after a myocardial infarction correlated well with those measured three months later. Moderate salt restriction is advisable. Early fluid intake is limited to 1,500 ml. to maintain an adequate urinary output of at least 800 ml. per day. A recent study showed that hot and cold liquids did not produce deleterious effects.

Bowel function. Opiates, bed rest, and change of diet predispose the patient to constipation. To prevent later straining, we prescribe a combination of 30 ml. of milk of magnesia and 100 mg. of dioctyl sodium sulfosuccinate (Colace) twice a day. Severe cathartics and enemas should be avoided. Bedpans are not used but use of a bedside commode is allowed. Our patients have bathroom privileges after 7 days, if there are no complications.

Bladder function. Urinary retention is especially common in elderly patients given opiates and is even more likely to occur if atropine is used for bradyarrhythmias. An indwelling catheter is used for a few days if urinary retention develops.

Anticoagulants. Anticoagulants are given to lessen thromboembolism. The frequency of the latter problem is highlighted by the demonstration of 39 per cent incidence of thrombosis of the calf veins during the acute phase of myocardial infarction using radioactive fibrinogen.[11] Another study with radioactive fibrinogen showed that anticoagulant treatment reduces the frequency of calf vein thrombosis from 22 to 6.5 per cent. However this study suggested that if early mobilization is followed, anticoagulation may be reserved for patients with evidence of thrombosis of veins or for patients who are confined to bed for more than a week. Another study showed that of 27 patients in good clinical condition, deep vein thrombosis detected by radioactive fibrinogen developed in only one patient, whereas thromboembolic complications occurred in seven of eight patients who were severely ill (i.e., manifested by hypotension, shock, or congestive he failure.) Recently the extensive literature anticoagulants was reviewed by Ribner a Frishman and by Chalmers and co-worke These authors concluded that the overwhelm majority of all trials favored anticoagulation a that all patients who present no specific contra dications should receive anticoagulants duri hospitalization for infarction. Ribner and c leagues further recommended low-dose hepa (5,000 units subcutaneously every 12 hours) f patients over 70 years of age and for those wi malignancy, severe hypertension, or preexistin gastrointestinal bleeding. This latter opinion w based on an extrapolation of the studies whi have shown that venous thrombi can be striking reduced after surgery by a well-controlled min heparin regimen. Future studies are necessary t clarify the use of low-dose heparin in patient with acute myocardial infarction. At present w recommend full-dose anticoagulation with wa farin during hospitalization and for several days thereafter if patients have had prior infarcts o thromboembolism, if the infarction appears larg as indicated by symptoms, physical findings, and laboratory findings, or if complications requiring prolonged bed rest such as congestive failure or hypotension are present. A collaborative study in which our group participated showed a higher survival rate and fewer bleeding complications among patients given warfarin alone than among patients receiving heparin alone or warfarin and

heparin. Furthermore, the risk of thromboembolism is not great during the first 24 to 48 hours of infarction and therefore early anticoagulation with heparin is not necessary

Dysrhythmia

As yet there is no full agreement about the use of antiarrhythmic drugs prophylactically in cases of acute myocardial infarction that present with a regular sinus rhythm. One study[71] showed that procainamide afforded highly significant protection against all types of ventricular arrhythmias, markedly reduced the need for acute therapy of arrhythmias, and prevented deaths from active arrhythmias, but the total number of deaths was the same as in the placebo group In this study patients with shock, heart block, or severe heart failure were excluded. Almost similar results were noted in a prophylactic study with quinidine.[72] Prophylaxis with disopyramide (Norpace) was associated with a decrease in ventricular arrhythmias, incidence of reinfarction, and mortality in a small group of unmonitored patients in an open ward.[73] Recently there have been several reports that propranolol may limit infarct size.[74] The National Institutes of Health is now sponsoring a multicenter study with propranolol in patients with acute myocardial infarction. This and other studies with propranolol may in the future give important information. Several studies[75-77] with prophylactic lidocaine showed a reduction in the frequency of ventricular tachyarrhythmias. In fact, Lie and co-workers[77] reported nine instances of ventricular fibrillation in a placebo group compared to no occurrences in the lidocaine group. In these studies the risk of ventricular fibrillation was not presaged by warning arrhythmias. Though not conclusive, we agree that such studies argue strongly for the use of lidocaine prophylactically A suggested prophylactic regimen with lidocaine consists of a loading dose of 200 mg. intravenously over a 20 minute period. Simultaneously with the loading dose an infusion of 2 to 4 mg. per minute is started and continued for at least 48 hours.[78] The loading dose and infusion rate are reduced by one-half if shock or heart failure are present.

Atrial arrhythmias

Atrial or junctional (nodal) premature beats may be associated with the development of heart failure or may be forerunners of atrial or junctional tachycardias. Atrial fibrillation or flutter are often preceded by premature atrial beats. If the premature atrial beats occur more frequently than 6 per minute and there is no heart failure or hypotension then they can be suppressed by giving 0.3 Gm. quinidine orally every 6 hours. If they occur in the presence of heart failure, then digitalis should be given.

The supraventricular tachyarrhythmias shorten diastole, compromise cardiac output, and may lead to extension of the infarction.[79] They tend to recur and classically are best treated with digitalis if the patient is hemodynamically stable. We prefer to use digoxin, giving 0.5 mg. initially and then 0.25 mg. every 2 to 4 hours until the ventricular rate is less than 100 beats per minute, regular sinus rhythm appears, or a total of 1.5 mg. has been given. In the presence of acute myocardial infarction, the heart is more sensitive to digitalis and extreme caution is necessary to avoid toxicity The first dose is usually given slowly intravenously the route of administration thereafter depends on the status of the patient. We use direct-current countershock initially if severe heart failure, cardiogenic shock, or persistent chest pain is present. Otherwise, it is reserved for patients who maintain a ventricular rate greater than 140 beats per minute in spite of digitalis or for those whose condition is beginning to deteriorate because of heart failure or hypotension If hypotension is present, the tachyarrhythmia may revert with elevation of the blood pressure by giving sympathomimetic agents as phenylephrine 10 mg. in 100 ml. of 5 per cent dextrose in water or metaraminol 100 mg. in 500 ml. of 5 per cent dextrose in water slowly intravenously In the absence of heart failure or hypotension and if the ventricular rate is over 140 beats per minute, some advocate the use of 1 to 2 mg. propranolol intravenously in divided doses 3 minutes apart, which may produce a regular sinus rhythm or slow the ventricular rate. Others prefer to use direct-current countershock initially for the supraventricular tachyarrhythmias, especially for atrial flutter which often is resistant to digitalis and is very sensitive to low-energy shocks.

Before direct-current countershock is used diazepam (Valium) is given intravenously to allay anxiety The dosage varies from 5 to 30 mg., usually the drug is given in increments of 5 mg. every five minutes until sedation appears adequate.

Recurrent atrial arrhythmias can be prevented

by giving maintenance digoxin daily or 0.3 Gm. of quinidine every six hours, or a combination of these Propranolol may also be required to prevent or control the ventricular response if trial arrhythmias recur

Ventricular ectopic arrhythmias

Premature ventricular beats. Premature ventricular beats are very common in patients with acute myocardial infarction. In the past, we did not institute therapy promptly unless the premature ventricular beats were more frequent than x per minute were multifocal or in pairs, or urred at the peak of the T wave (R on T phenomenon) of the preceding beat. Recent stud have shown that R on T is not a critical determin nt of primary ventricular fibrillation. I additi n Roberts and co-workers[23] reported hat repetitive ventricular arrhythmias in patients with acute myocardial infarction are often precipitated by late rather than by early premature ventricular complexes. Furthermore, warning arrhythmias were found by Lie and colleagues in only 60 per cent of patients in whom ventricular fibrillation developed. These data suggest that lidocaine prophylactically should be given to all patients with an infarction. No clear definition is available at present regarding the nature and type of ventricular beat that should be prevented or suppressed. However it appears to us that therapy should be initiated at the first indication of any type of premature ventricular beat, irrespective of its time in the cardiac cycle

Lidocaine hydrochloride (Xylocaine) is the drug of choice. In order to administer it properly it is important to understand the pharmacokinetics of lidocaine. The half life of lidocaine's distributional phase is 8 minutes and that of the elimination phase is 108 minutes. Accordingly there may result a significant drop in blood level between the peak serum level from the initial bolus (rapid distribution) and the subsequent steady state from the constant infusion which may take up to 5 to 7 hours. Thus a significant interval when plasma levels are inadequate can exist and ventricular ectopy can occur This cannot be corrected by increasing the concentration or the rate of the constant infusion Several studies[24, 25] utilizing plasma levels have shown that this subtherapeutic hiatus can be vercome without developing toxicity by giving a loading dose of 75 to 100 mg. lidocaine bolus initially followed by 50 mg. every 5 minutes for up to a total of 200 to 225 mg. or by giving this total amount as an infusion in 10 to 20 minutes. We have found both of these loading methods satisfactory Simultaneously a constant infusion of 2 to 4 Gm. lidocaine in a liter of 5 per cent dextrose in water should be started at a rate of 1 ml. per minute. If other ventricular arrhythmias occur during the infusion, another bolus of 50 to 100 mg. can be given. These doses should be reduced by one-half if shock or heart failure are present or if the patient is over 70 years of age.

If lidocaine is ineffective, procainamide hydrochloride (Pronestyl) propranolol (Inderal), or diphenylhydantoin sodium (Dilantin) can be given.

Because lidocaine can affect the central nervous system, producing such side effects as euphoria, depression, or grand mal seizures, the constant infusion dosage should not exceed 5 mg. per minute. Also since lidocaine is metabolized i the liver it should be given cautiously in the presence of liver congestion as due to heart failure and shock. From 24 to 48 hours before discontinuing the lidocaine drip, 375 to 500 mg. of procainamide is given orally every four to six hours or 300 mg. of quinidine sulphate every six hours at least throughout hospitalization. If these agents are ineffective in preventing recurrence of premature ventricular beats, then 100 to 200 mg. disopyramide phosphate (Norpace) or 10 mg. of propranolol given orally every six hours can be tried. The propranolol dosage can be increased provided side reactions do not occur Occasionally a combination of these drugs is necessary Common early side reactions are fever from procainamide and diarrhea, nausea, and vomiting from quinidine sulfate. Disopyramide, because of its anticholinergic effect, can produce urinary retention. Since it is excreted by the kidneys, it should be given cautiously and in smaller doses in the presence of kidney disease. It also can aggravate heart failure. Its action is essentially the same as quinidine, but it does have less gastrointestinal side effects. Propranolol must be used with caution if incipient failure is present or if the patient is diabetic. It is contraindicated in A V block, bronchial asthma, and severe heart failure. If these drugs do not terminate the premature beats, potassium should be tried, for hypokalemia may be a factor. At times the serum potassium level may be

normal, yet there may be an intracellular deficit.

Ventricular tachycardia Bursts of three or more consecutive premature ventricular beats that usually occur at a rate of 120 to 250 per minute constitute paroxysmal ventricular tachycardia according to the criteria of the American Heart Association. This arrhythmia is usually intermittent and non sustained in acute myocardial infarction, and the initial and maintenance therapy is the same as for premature ventricular beats.

A small group of patients have sustained attacks of ventricular tachycardia. A sharp blow over the precordium may terminate an attack. Vasopressors may revert the rhythm to regular sinus if hypotension is controlled. Next, if a 100 mg. dose of lidocaine given intravenously fails to reverse the arrhythmia, we proceed with synchronized direct-current precordial shock. If the latter treatment is not available, we suggest that after a few minutes a second 100 mg. dose of lidocaine be given, followed by 50 mg. of procainamide given intravenously every minute, the total dosage not to exceed 0.5 Gm. If reversion occurs before the total dosage is reached, injections are discontinued. If it does not occur 0.5 to 1 mg. of propranolol intravenously every 3 minutes for not more than three doses or 100 mg. diphenylhydantoin (Dilantin) intravenously can be tried. If chest pain, congestive heart failure, shock or hypotension is present, direct-current cardioversion (if available) should be used immediately rather than antiarrhythmic drugs, which can cause further myocardial depression.

Accelerated idioventricular rhythm This generally benign paroxysmal ventricular arrhythmia has rates ranging from 60 to 120 beats per minute. It has been noted in up to 20 per cent of cases since the advent of continuous monitoring and has been given a variety of names, such as slow ventriculr tachycardia, paroxysmal ventricular tachycardia, non paroxysmal ventricular tachycardia, and accelerated idioventricular rhythm. It often appears with an inferior infarction with sinus bradycardia and sinus arrhythmia. It is frequently seen during sleep, when the sinus rate is even slower. Accelerated idioventricular rhythm usually begins as a late end-diastolic ventricular ectopic beat, escape beat, or as a fusion beat. It disappears as the rate of the sinus rhythm exceeds the rate of the ectopic rhythm. If both occur at the same rate, fusion complexes result. The paroxysms are usually only four to 30 beats. Accelerated idioventricular rhythm is usually benign, does not lead to ventricular fibrillation, often clears with no medications, and will respond to atropine which should be given if hypotension or heart failure develops. Cardiac pacing is seldom necessary. At times this arrhythmia may coexist with ventricular tachycardia in the same patient[76] or it may represent ventricular tachycardia with an exit block. In the latter instance, a slow ventricular rate can increase, suddenly double or become a multiple of a more rapid rate or the exit block can present as a Wenckebach grouping. A recent study considered the arrhythmia to be slow ventricular tachycardia if it started with a premature ventricular beat, the rhythm was irregular and it terminated suddenly.[77] These variations should be treated in the same manner as was described for ventricular tachycardia.

Ventricular fibrillation Ventricular fibrillation can occur suddenly and unexpectedly often in the patient who seems to be doing well with no evidence of pump failure (primary type). Unless there is underlying heart block, ventricular fibrillation is seldom self limiting. Defibrillation should be done immediately (since the patient is being monitored in the cardiac unit) without delay for drug therapy or cardiac massage. Usually reversion to sinus rhythm is successful unless the patient has the secondary type of ventricular fibrillation with circulatory failure (intractable heart failure or shock).

If cardiac arrest persists after several direct current shocks, 44.6 mEq. of sodium bicarbonate is given intravenously and repeated as is necessary to combat acidosis during the resuscitation. Serial pH determinations should be done, for excessive sodium bicarbonate may produce metabolic alkalosis, precipitate congestive failure, and cause hyperosmolality in a range that is potentially detrimental to cerebral function.[78] It should not be given unless ventilation is adequate. After two ampules are given, the pH should be determined and more is administered if the patient is acidotic. Repetitive electric shocks may not be effective particularly when fine fibrillatory waves appear on the electrocardiogram. These cases may be more responsive to electric shock if an intravenous injection of 5 ml. of a 1 10,000 solution of epinephrine is given which produces

large fibrillatory waves. In some refractory cases, intravenous injection of 50 to 100 mg. of lidocaine alone or with the epinephrine may aid defibrillation. Next, 1 mg. of propranolol intravenously may be tried. Bretylium tosylate (Bretylol), an antiadrenergic agent is now available for clinical use. One study showed that ventricular fibrillation may be terminated with DC shock after the administration of a single intravenous bolus of bretylium tosylate (5 mg./Kg.) following the failure of conventional resuscitation efforts. After reversion to a sinus rhythm, continuous infusion with lidocaine should be given for maintenance antiarrhythmic therapy and later procainamide, quinidine, propranolol or disopyramide therapy such as that described for premature ventricular beats and ventricular tachycardia, can be administered.

Drug-resistant ventricular arrhythmias Ventricular arrhythmias refractory to all drug therapy in the absence of atrioventricular block have been reported. These arrhythmias (premature ventricular beats, ventricular tachycardia, flutter and fibrillation) recurred in spite of adequate antiarrhythmic drugs. Both rapid atrial and ventricular transvenous pacing have been effective in overdriving and preventing such arrhythmias. At times, pacing combined with antiarrhythmic drugs may be necessary to control recurrent ventricular tachyarrhythmia.

Arrhythmias at the time of discharge Ventricular arrhythmias encountered within the first few days in the coronary care unit fail to identify patients likely to have these at the time of discharge and in some studies have not been important in predicting long term survival. However Conley and colleagues reported an excess mortality rate after hospital discharge in patients with acute myocardial infarction complicated by ventricular fibrillation in the coronary care unit. Other reports suggested that ventricular arrhythmias present at discharge appeared to have a worse prognosis compared to those occurring during the first few days after admission. In view of these findings predischarge Holter recordings should be made. At present there is no agreement on how long a patient should be monitored. Ruberman and associates monitored on hour for ectopic activity. Others have suggested 6 to 24 hours. Currently some patients are being stress tested at a low level of exercise prior to discharge. The exercise electrocardiogram provides a small increase in the detection of serious arrhythmias that needs further studies to evaluate its usefulness. All studies agree that the presence of complex premature beats (R on T runs of two or more, multiform, bigeminal, more than five per minute) at the time of discharge is associated with an increased risk of sudden coronary death at least three times that of patients free of these. Kotler and co-workers noted that after infarction 16.8 per cent of patients on Holter monitoring had parasystole and that none of these patients died in the follow-up period. This study needs further confirmation and indicates that distinguishing types of premature ventricular beats may be very important in regard to long term therapy. Our policy at present is to Holter monitor patients for 24 hours (off of antiarrhythmic drugs) predischarge, and if complex premature ventricular beats are present, treat them for at least one year until further data are available. At the end of the third month post infarction, the Holter monitoring should be repeated. The one year mortality rate of patients surviving 30 days is nearly twice that of any subsequent year through the fifth year. At present there is no agreement with regards to the type of therapy. Long term procainamide can produce reactions, namely a lupus-like syndrome. Therefore we prefer to begin with quinidine, and if patients cannot tolerate this or if it is ineffective, then change to propranolol or disopyramide. The multicenter study with propranolol may in the future give important information. A recent cooperative study with practolol reported twofold reduction in sudden death in treated survivors of anterior infarction compared with a control group. However practolol is no longer available because of its side effects.

Bradyarrhythmias

Sinus bradycardia Sinus bradycardia is most commonly observed in patients with inferior myocardial infarction. The heart rate is under 60 beats per minute, and the slowness may be followed by escape beats and by slow junctional (nodal) rhythms or even by cardiac standstill. The long diastolic pauses favor the development of ventricular arrhythmias (premature ventricular contractions, ventricular tachycardia, ventricular fibrillation). In addition, these patients are prone to vasovagal attacks characterized by pallor nausea, at times confusion slow heart

rate, and a fall in blood pressure. Morphine may precipitate or aggravate such attacks.

At one time atropine was given to all patients with sinus bradycardia secondary to acute myocardial infarction to prevent the above complications. However Epstein and associates[3] show that in dogs sinus tachycardia may precipitate serious ventricular arrhythmias and that slow rates may be protective. Therefore if the patient has a moderate level of bradycardia and is stable it is best not to give atropine. Other studies, with which we agree, have shown that if the rate is below 50, and if ventricular arrhythmias, heart failure, or hypotension are present, atropine can be of benefit.[13] The usual dose initially is 0.5 or 0.6 mg. intravenously. The total accumulative dose should not exceed 2.5 mg. over 2.5 hours. Smaller doses than 0.4 mg. may produce a paradoxical slowing of the rate. In the event excessive sinus tachycardia (more than 100 beats per minute) or ventricular arrhythmia occur, the rate can be slowed by the use of propranolol. In addition, atropine can produce urinary retention, glaucoma, and mental confusion. Raising the legs may also aid in alleviating the vasovagal attacks by increasing venous return and stretching the right atrium and by increasing the arterial pressure. Thus the sinus rate is increased (Bainbridge reflex) by reducing vagal tone. Occasionally, temporary transvenous pacing of the right atrium may be necessary, especially if there is circulatory collapse.

Atrioventricular conduction disturbances. Atrioventricular conduction disturbances were also seen most often in patients with inferior myocardial infarction and are usually due to a vagal component and reversible ischemia. We do not treat first-degree A V block. It remains controversial whether a temporary demand mode transvenous pacer should be inserted if second- or third-degree A V block occurs with an inferior infarction. The over all mortality rate for inferior infarction and third-degree A V block is 20 to 40 per cent. However, Rotman and colleagues showed that if heart failure or shock were absent, then the mortality rate is only 11 per cent, and this group was at no higher risk of mortality than were others without block. We do not insert a temporary pacing catheter in patients with an inferior infarction and second- or third-degree A V block unless the patient's ventricular rate is 40 or below, his condition is deteriorating (hypotension, heart failure, ventricular arrhythmias), dizziness or syncope occurs, or if complete heart block exists with a wide QRS complex. Insertion of a catheter in most cases requires fluoroscopic guidance, although some physicians have inserted floating catheters at the bedside without such control. Before the catheter is removed, sinus rhythm should be present for several days. Seldom can it be removed sooner than one week. Corticosteroids are of questionable value, but are used.

Heart block due to extensive septal infarction is usually associated with an anterior myocardial

Table I Comparison of features of third-degree AV block in inferior and anterior infarcts

	Inferior	*Anterior*
Pathology	Edema of AV node or His bundle	Infarction of septum involving bundle branches
Onset	slowly	sudden
QRS width	narrow	wide
Vent. rate	45 or above	below 45
Associated with Mobitz type II	rare	common
Adams-Stokes	rare	common
Mortality	20-40%	75%
Hemodynamic effects	usually none	circulatory failure

Table II Indications for temporary pacemaker insertion in patients with anterior infarctions

Usual
- Second degree or complete A V block
- New RBBB + LAH
- New RBBB + LPH
- New alternating RBBB and LBBB
- New BBB with 1° A-V block

Possible
- New RBBB
- New LBBB
- Old RBBB + LAH + 1° AVB
- Old RBBB + LPH + 1° AVB
- Old alternating RBBB and LBBB + 1° AVB

No
- Old LBBB, Old RBBB — Regardless of PR interval
- Old RBBB + LAH
- Old RBBB + LPH
- Old alternating RBBB and LBBB

Abbreviations: RBBB = right bundle branch block, LAH = left anterior hemiblock; LPH = left posterior hemiblock; LBBB = left bundle branch block.

Table III Outline of treatment of arrhythmias associated with acute myocardial infarction

Type of arrhythmia	Recommended treatment
Supraventricular	
Premature atrial or junctional beats (nodal)—6 or more per minute	Quinidine 200-300 mg. every 6 hours. If there is associated heart failure or hypotension, digitalis
Atrial or junctional (nodal) tachycardia, atrial flutter atrial fibrillation	Digitalis or DC shock. If condition is deteriorating, direct-current shock should be tried first
Sinus tachycardia	Digitalis if in failure. If patient is not in overt failure, propranolol, 5-10 mg. every 6 hours
Ventricular	
Ventricular ectopic beats	Lidocaine, 5-100 mg. bolus I.V. and then 50 mg. every 5 minutes for 3 doses, or initially give 200-225 mg. I.V. over a 20 minute period
Ventricular tachycardia (sustained)	Lidocaine, 100 mg. bolus I.V. repeat in two minutes. If ineffective, then direct-current shock. If latter is unavailable, procainamide, 50 mg. I.V. every minute up to 0.5 Gm. or propranolol 0.5 mg. to 1 mg. every 3 minutes up to 3 doses or dilantin, 100 mg. I.V.
Prevention of recurrences of ventricular arrhythmias	Drip of 2 to 4 Gm. of lidocaine per liter of 5 per cent glucose in water 1 ml. per minute for 48 hours. Then procainamide 375-500 mg. every 4 to 6 hours, quinidine, 300 mg. every 6 hours, propranolol, 10-40 mg. every 6 hours or disopyramide 150 to 200 mg. every 6 hours orally. Bretylium tosylate, 5 mg./Kg. I.M. every 6-8 hours
Drug-resistant ventricular arrhythmias	Transvenous atrial or ventricular pacing. Rarely surgery

Table III Continued

Type of arrhythmia	Recommended treatment
Accelerated idioventricular rhythm	None, or atropine, 0.6 to 0.8 mg. I.V. as needed. Rarely cardiac pacing
Bradyarrhythmias	
Sinus bradycardia or arrest	Atropine, 0.6 to 0.8 mg. I.V. as needed, if rate below 50/min., hypotension, heart failure or ventricular arrhythmias occur. Rarely atrial pacing
Inferior infarction	
First-degree atrioventricular block	None
Second- and third-degree atrioventricular block	None if patient is stable. If rate below 40, QRS wide, hypotension, ventricular arrhythmias, syncope or heart failure is present, then insert standby transvenous pacer
Anterior infarction with bundle branch block and A-V block	See Table II
Cardiac arrest	
Ventricular fibrillation	Adequate ventilation. External cardiac massage. Immediate direct-current shock. Lidocaine, 100 mg. I.V. Epinephrine, 5 c.c. of 1:10,000 solution I.V. Sodium bicarbonate, 44.6 mEq. I.V. Propranolol, 1 mg. I.V. Bretylium tosylate, 5 mg./Kg. I.V.
Ventricular standstill or slow idioventricular (agonal) rhythm	Thump chest. Adequate ventilation. External cardiac massage. Epinephrine, 5 c.c. of 1:10,000 solution I.V. Sodium bicarbonate, 44.6 mEq. I.V. Isoproterenol, 0.02 mg. I.V. Calcium chloride, 5 c.c. of 10 per cent solution I.V. Rarely percutaneous or transvenous pacing

infarction and has a mortality rate up to 75 per cent. Most often in such cases the level of the block is infranodal. This type of block is often preceded by conduction impairments in various combinations involving the right bundle and the two fascicles of the left bundle. Table I compares the features of third-degree A-V block in anterior and inferior infarctions.

Trifascicular block is impending if right bundle branch block occurs with extreme left axis (about −60 degrees) or right axis (about +120 degrees) deviation, especially if such axes occur intermittently in the same patient. The left axis indicates block of the left anterior superior fascicle of the left bundle (left anterior hemiblock), and the right axis, block of the left posterior inferior fascicle of the left bundle (left posterior hemiblock). Also any type of bundle branch block with first degree A-V block or alternating right and left bundle branch block can precede trifascicular block. These various combinations can progress to complete A-V block on an average of about 4

per cent.[13] This progression can be sudden and often unheralded. Somewhat unexpected is the incidence of progression of pure right bundle branch to complete block in 43 per cent of patients and of left bundle branch block in only 20 per cent of patients.[14] A recent collaborative study by Hindman and co-workers[14] described the clinical significance of bundle branch block complicating acute myocardial infarctions and the indication for temporary and permanent pacemaker insertion. Table II lists our present indications for insertion of a demand mode transvenous pacemaker if bundle branch block or heart block occurs in a patient with an anterior infarction. The high mortality rate has not been significantly changed by temporary pacing, but as mentioned by Hindman and associates, A strictly statistical argument ignores the mechanism of dying for patients with and without prophylactic temporary pacing. Bifascicular block progresses to complete heart block at a rather high rate. In the collaborative study nine patients died as a result of sudden development of complete heart block in the hospital. Standby pacing in bifascicular block must prevent some of the mortality due to the sudden development of complete heart block, even though death from pump failure will continue to be high. In addition, temporary pacing may be of value in treating the frequent ventricular arrhythmias observed in such cases by the use of continuous Holter monitoring.[14]

Patients with inferior infarction and A V block seldom require a permanent pacer however among those with anterior infarction and its low level of block a few have permanent block and require a permanent pacer Some studies advocate permanent pacemakers in all patients with anterior infarctions who develop high degree A V block (Mobitz type II A V block or third-degree A V block) even though the high degree block may be transient, since sudden late deaths are common in such patients.[13] At present we agree with this policy

Ventricular asystole. Ventricular asystole or slow idioventricular rhythm (agonal) is usually associated with pump failure. If the heart beat is not restored after a sharp blow to the chest, closed-chest cardiac massage should be started along with adequate pulmonary ventilation. Next, 5 ml. of a 1 10,000 solution of epinephrine is injected intravenously If asystole persists, an 0 02 mg. dose of isoproterenol is injected intravenously and is followed by 5 ml. of a 10 per cent solution of calcium chloride. Sodium bicarbonate, 44.6 mEq., should be given as is necessary during resuscitation to combat acidosis with the same precautions noted for cardiac arrest due to ventricular fibrillation. Transvenous pacing or direct percutaneous puncture of the heart with a needle electrode may be tried, although it is usually ineffective unless the ventricular asystole is intermittent with underlying complete A V heart block.

Table III outlines the treatment of arrythmias associated with acute myocardial infarction.

Other complications

Congestive heart failure. Left ventricular failure of varying degree is common in the majority of patients during the first week after onset of infarction. Left heart failure may occur with a normal-sized heart, with normal pulse rate, and in the presence of a normal central venous pressure. Subtle symptoms and signs are often present before overt evidence of congestive heart failure. Some of these subtle findings are a positive hepatojugular reflux, ventricular (S_3) gallop rhythm, paradoxical splitting of the second sound, pulsus alternans, sinus tachycardia over 110 beats per minute, weakness, coughing (especially on lying flat) Cheyne-Stokes respiration, wheezing instead of râles, and pulmonary interstitial edema on x ray A portable chest x ray has limitations, yet it may demonstrate early evidence of left ventricular failure. On x ray there may be dilatation of upper lobe vessels due to increasing shunting of blood, loss of normal sharp hilar markings, increased interstitial density of lungs and confluent areas of edema. Less often, one may note thickening of the interlobular fissures, dilatation of the right descending branch of the pulmonary artery and interlobar or mild pleural effusions. Dyspnea, râles, deep jugular vein pulsations and external jugular distension, hepatomegaly and edema are late findings of heart failure.

Patients with a normal-sized heart and evidence of mild failure during the initial few days of infarction usually require no therapy Diuretics may be given in small doses to avoid a brisk diuresis which can rapidly lower the left ventricular filling pressure with a fall in cardiac output and the development of hypotension. The use of digitalis in myocardial infarction remains con

troversial. Patients in heart failure with cardiomegaly congestion that does not respond to diuretics alone, or an S gallop should be given digitalis. It should be administered cautiously since these patients are more sensitive to the drug and prone to toxicity especially arrhythmias. We would prescribe two-thirds of the usual loading dose. The clinical state dictates the method rate, and route of administration. We often begin with 0.5 mg. digoxin orally and then give 0.25 mg. every four hours for one or two more doses, maintaining the patient on 0.25 mg. daily provided renal function is adequate. If necessary this dosage can be given more rapidly intravenously. In the absence of monitoring of the pulmonary arterial and wedge pressures by use of the Swan-Ganz catheter one must exhibit good clinical judgment as to the response of the patient to digitalis and diuretics. Studies have shown that pulmonary congestion is rare when the pulmonary capillary wedge pressure is below 18 mm. Hg. McHugh and colleagues reported that x ray changes correlate reasonably well with hemodynamics, but there may be abnormal wedge pressure elevation initially in the absence of x ray changes and there may be a post therapeutic lag on x ray findings.

If pulmonary edema occurs, the patient should be in the Fowler's position and oxygen should be administered. Intramuscular or at times, intravenous administration of 6 to 12 mg. of morphine sulfate is useful to slow exaggerated respirations, produce venous pooling of blood, and allay apprehension. In the event of an inferior infarction, one should be cautious since the vagomimetic effect of morphine may precipitate or aggravate heart block. We administer digitalis immediately although some consider this useful initially only if supraventricular arrhythmias are also present. Immediate increase in venous capacitance and later diuresis can be produced by administering 40 mg. of furosemide (Lasix) intravenously. Electrolyte levels should be checked often, since potassium loss may be significant. If the patient does not respond to these measures and is not hypotensive, then vasodilator therapy may be tried in an attempt to reduce preload (left ventricular filling pressure) and afterload (systemic impedance) which are important determinants of myocardial oxygen consumption. Initially sublingual nitroglycerin or isosorbide dinitrate can be started which predominantly cause venodilation and reduce preload and pulmonary congestion but have less effect on systemic impedance and therefore produce minimal alterations of cardiac output. If improvement is not achieved, then sodium nitroprusside, which affects both preload and afterload, can be given intravenously. However we would not give nitroprusside unless the patient's pressures can be monitored by a Swan-Ganz catheter. The dosage should be titrated to lower the pulmonary capillary wedge pressure to an optimal level (14 to 18 mm. Hg) without lowering the systemic arterial pressure below 95 mm. Hg. Unfortunately today many are inserting Swan-Ganz catheters and beginning nitroprusside as their first therapeutic measure prior to trying the usual proven methods of therapy. Complications reported with the Swan-Ganz catheter include knotting of the catheter, ventricular arrhythmias, pulmonary infarction, balloon rupture, formation of thrombi on the balloon and catheter and thrombophlebitis and infections at the cutdown site.

If the patient with infarction develops chronic refractory heart failure which does not respond to digitalis and diuretics, then long term vasodilator therapy can be tried. When pulmonary congestion is the principal problem a long-acting vasodilator such as nitroglycerin ointment, which affects preload, is preferable. A reflex arteriolar constriction in heart failure maintains the blood pressure in the presence of a low cardiac output. This increased afterload further impairs ventricular emptying. An arterial vasodilator such as hydralazine which affects afterload, is the drug of choice when the primary defect is a reduction of cardiac output, but it has the disadvantage of producing many side effects. Prazosin, a vasodilator antihypertensive agent, reduces both preload and afterload and can be used as the only drug instead of the combination of a nitrate and hydralazine. However prazosin may produce a first dose reaction (hypotension and faintness) and tachyphylaxis can develop. Regardless of the type of vasodilator therapy it should be used cautiously to avoid hypotension.

Cardiogenic shock. Cardiogenic shock should be correctly defined. Often the blood pressure may drop below 90 mm Hg, yet the patient is warm and has adequate urinary output and is not in shock. The patient in shock is usually cold and clammy and the urine output is less than 0.5 ml per minute. The hemodynamics of shock can vary

rapidly in the same patient. Therapy should be varied according to the hemodynamic findings. Ideally a Swan-Ganz catheter should be inserted at the bedside via a peripheral vein to measure pulmonary artery and pulmonary capillary wedge pressures and cardiac output (thermodilution technique). The pulmonary artery end-diastolic and wedge pressures usually reflect left ventricular filling pressure, whereas the central venous pressure reflects right ventricular filling pressure. The pulmonary capillary wedge pressure and the cardiac output studies have been useful in identifying subsets that may respond differently to various forms of therapy.[66] We realize that infarction is mainly a left ventricular disease, but we will include the central venous pressure in this discussion of subsets, since as will be mentioned later it may be helpful. Elevated central venous and pulmonary wedge pressures with low cardiac index is one of the combinations noted in shock. The pulmonary wedge pressure will be over the top optimal level of 18 mm. Hg. In such cases it is best to increase the cardiac output by direct effect on the myocardium by the use of an inotropic agent such as dopamine hydrochloride (Intropin) and by reducing the preload and afterload by the use of sodium nitroprusside. Dopamine is a naturally occurring catecholamine which increases contractility and cardiac output and is preferably used in patients who are mildly hypotensive (blood pressure usually 80 mm. Hg or above). It produces less tachyarrhythmias and it increases renal blood flow which are advantages over isoproterenol (Isuprel). Administration is begun intravenously at doses of 2 to 5 mcg./Kg./minute. Nitroprusside should only be given if the arterial pressure is greater than 95 mm. Hg. and requires extreme caution and constant monitoring. Usually we begin with 0.5 mcg./Kg./minute. L-norepinephrine (Levophed) and metaraminol (Aramine) increase contractility and these also increase peripheral vascular resistance. Such vasopressor therapy is begun initially if there is severe hypotension, in an attempt to raise the systolic pressure to about 100 mm. Hg. If the central venous pressure is normal and the pulmonary wedge pressure is elevated, essentially the same therapy is advised as described above when both of these parameters are elevated. If the central venous pressure and the pulmonary wedge pressure are normal or low the plasma volume should be expanded with agents such as dextran. The wedge pressure should be maintained above normal at optimal range (14 to 18 mm. Hg) in order to maintain or increase the cardiac output by the Frank-Starling mechanism.

In the event the response to therapy is not dramatic, then the patient should be supported with counterpulsation by use of the intra-aortic balloon. The inflated balloon during diastole allows for better coronary perfusion. Its also reduces afterload with resultant decrease in myocardial oxygen requirement. The aim is to maintain systolic blood flow reduce the load on the heart, and improve myocardial contraction. If the patient, despite hemodynamic stabilization, cannot be weaned from the mechanical support, then in some centers coronary arteriography followed by saphenous vein grafts with or without aneurysmectomy or infarctectomy are attempted.[67]

These sophisticated methods today should be limited primarily to research medical centers or to larger community hospitals that have appropriate equipment and specially trained personnel. The practicing physician can use the central venous pressure (or observe the neck veins), blood pressure, urinary output, and his clinical judgment in therapy of shock. Even though most infarctions involve the left ventricle, the central venous pressure which reflects the right ventricular filling pressure may be a value. If the central venous pressure is normal or low the patient can be challenged with intravenous dextran, realizing that the pulmonary wedge pressure may be high and that the patient's condition may worsen. Sudden elevation of the central venous pressure (over 5 cm. of H_2O) or the appearanceof dyspnea should alert one to this latter problem. If the central venous pressure is elevated, most often the pulmonary wedge pressure will be above the optimal range (except in a few instances primarily of inferior infarction) and therefore therapy should be the same as mentioned previously when these two pressures are elevated. However vasodilator therapy should not be given without pulmonary capillary pressure and cardiac output monitoring. There have been conflicting reports of the value of large doses of steroids in cardiogenic shock. Arterial pH should be monitored since metabolic acidosis develops rapidly in shock and this condition should be corrected by the use of sodium bicarbonate.

Embolism Embolism has become a rather uncommon complication of acute myocardial infarction, probably because of the use of anticoagulants and the institution of early ambulation. Early recognition of pulmonary emboli can be very difficult. Often one waits for classic lung findings or evidence of phlebitis. One should be suspicious of pulmonary emboli if a patient has periods of hypotension, tachypnea, tachycardia, fever or low arterial O oxygen tension. On the other hand, massive pulmonary embolism can occur in the absence of dyspena, cyanosis, or hypotension.[a] If pulmonary emboli occur in spite of well-controlled oral anticoagulation we would change to heparin The source of the emboli is usually the veins in the legs or lower abdomen. Ligation or clipping of the inferior vena cava or transvenous insertion of an umbrella filter are seldom required in acute myocardial infarction. Peripheral arterial emboli can be extracted by the use of a Fogarty catheter (balloon catheter) through remote arteriotomy incisions under local anesthesia.

Heart murmurs The most common causes of heart murmurs in myocardial infarction are papillary muscle dysfunction or rupture, rupture of the interventricular septum or rarely rupture of chordae tendineae Rupture of the septum produces a pansystolic murmur and thrill along the left lower sternal border and it is occasionally maximal at the apex and may be confused with the murmur of papillary muscle rupture. Rupture of the papillary muscle is less often associated with a thrill. The over all mortality rate for rupture of the ventricular septum is 24 per cent within the first day and 65 per cent in the first two weeks, and for papillary muscle rupture 50 per cent and 80 per cent for the same periods of time.[a] Catheterization studies should be done if surgery is considered since clinical differentiation of these lesions can be difficult The diagnosis can be made at the bedside with the Swan-Ganz catheter It is usually best to delay surgery for at least four weeks to allow time for healing. Heart failure should be controlled with digitalis and diuretic therapy Afterload reduction with nitroprusside infusion may aid Pulmonary capillary wedge and intra arterial pressures should be monitored during vasodilator therapy Dopamine should be started for hypotension However if the patient s condition is deteriorating despite adequate care immediate surgical repair should be considered. Prior to surgery an intra-aortic balloon is usually inserted and often continued postoperative. In addition to repairing the mechanical lesion aortocoronary bypass grafting to suitable arteries should be performed.

Recurrent pain Soon after an infarction a patient may have recurrent chest pain. Pericardial pain should be excluded for it may be present even though a pericardial rub is not audible. If the pain is considered to be ischemic then the patient may be at risk for extension of the infarction or reinfarction. Intensive therapy with nitrates and propranolol should be given. Rarely the pain cannot be controlled and then coronary angiography and coronary bypass surgery should be considered.

Post-myocardial infarction syndrome. The post-myocardial infarction syndrome (Dressler's syndrome) is a recurrent febrile illness with pericarditis, pleuritis, and pneumonitis. It should not be mistaken for pulmonary embolism or recurrent myocardial infarction. It can occur anytime after the first week following an acute myocardial infarction and may be recurrent up to one year A pericardial rub is often present with a transmural infarction within 36 to 48 hours and usually clears in three to five days. If it persists longer the Dressler syndrome may be developing. Anticoagulants should be discontinued in the presence of this syndrome, since pericardial hemorrhage and even cardiac tamponade can occur The treatment is symptomatic with aspirin or indomethacin (Indocin) unless the syndrome persists or recurs, in which case steroids may be tried. Rarely after recurrent attacks in spite of therapy the pericardium should be resected.

Investigative forms of therapy for acute myocardial infarction continue actively Several approaches to decrease infarct size have been reported and recently have been reviewed in a series of articles by Hillis and Braunwald. Review of the literature does not provide conclusive evidence that treatment with polarized solution (glucose-insulin-potassium), hyaluronidase, nitroglycerin and other vasodilators, steroids, propranolol, or intra aortic balloon counterpulsation reduces infarct size. Analysis of serial CPK determinations, ST segment mapping, and radioisotope studies have been used for assessing infarct size or extension. These measuring techniques have significant limitations and are not entirely satisfactory to judge the efficacy of inter-

ventions. These various interventions should not be used routinely until further data are available to determine their effect on morbidity and mortality

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Appraisal and reappraisal of cardiac therapy

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Clinical pharmacology of the new beta adrenergic blocking drugs Part 2 Physiologic and metabolic effects

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After two decades since their discovery the therapeutic use of beta-adrenoceptor blocking drugs in angina pectoris, cardiac arrhythmias, and hypertension has been well established. Beta blockers are also being used for a growing number of new indications.

Some of the basic pharmacodynamic and pharmacokinetic *differences* between beta-blocking agents have been discussed in the *previous* article. The main emphasis of this article will be directed toward the drugs and their physiological and metabolic effects in man.

Cardiovascular effects

Effects in hypertension (Tables I and II) It is now well recognized that beta adrenergic blockers are effective in controlling the blood pressure of many patients with hypertension. At the present time there is no consensus of opinion on the mechanism or mechanisms whereby these drugs lower blood pressure. It is probable that some or all of the following play a part

1. Slowing of the heart rate and some decrease in myocardial contractility (negative chronotropic and inotropic effects) lead to a decrease in cardiac output, which, in the long term may lead to a reduction in blood pressure. It might be expected that this factor may be *of* particular importance in hypertension related to a high output state.

2. Central nervous system effect. There is good clinical and experimental evidence that β-blockers enter the central nervous system. The occurrence of dreams, insomnia, hallucinations, and depression during therapy with beta blockers supports this conjecture.

Infusion of l and dl propranolol into the cerebral ventricles of conscious rabbits caused a marked antihypertensive effect, whereas d propranolol caused the blood pressure to rise. By injecting drugs into the vertebral arteries of anesthetized dogs, other investigators found a central antihypertensive action for alprenolol but not for propranolol. Although there is little doubt that beta blockers (especially those with high lipophilicity e.g., alprenolol, propranolol) enter the central nervous system in high concentrations, an antihypertensive effect mediated by their presence is not yet well *defined.*

3. Differences in effects on plasma renin. The relationship between the hypotensive action of beta-blocking drugs and their ability to reduce plasma renin activity is currently one of the more hotly disputed areas in the field of hypertension. There is no doubt that beta-blocking drugs can antagonize sympathetically mediated renin release. However adrenergic activity is not the only mechanism whereby renin release is mediated. Other major determinants are sodium balance posture, and renal perfusion pressure.

Laragh and his group[4] have suggested that a decrease in renin output by the kidney is the major factor in the antihypertensive effect of β-blockers. Propranolol lowers plasma renin activity in normal[7] and hypertensive subjects[8]

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Table I Pharmacodynamic properties and cardiac effects of beta-adrenoreceptor blocking drugs

Drug	*Cardio-selec tivity**	*Partial agonist activity*	*Membrane stabilizing activity*	*Resting heart rate*	*Rate of heart rate increment in response to exercise*	*Myocardial contractility*	*Resting blood pressure*	*Resting atrio-ventricular conduction*	*Anti-arrhythmic effect*
Acebutolol	+	+	+	↓	↓	↓	↓	↓	
Alprenolol	0	+ +	+	↓ ↔	↓	↓↔	↓	↓ ↔	
Atenolol	+	0	0	↓	↓	↓	↓	↓	+
Metoprolol	+	0	±	↓	↓	↓	↓	↓	+
Oxprenolol	0	+ +	+	↓ ↔	↓	↓↔	↓	↓ ↔	+
Pindolol	0	+ + +	+	↓ ↔	↓	↓↔	↓	↓ ↔	+
Practolol	+	+ +	0	↓ ↔	↓	↓↔	↓	↓ ↔	+
Propranolol	0	0	+ +	↓	↓	↓	↓	↓	
Sotalol	0	0	0	↓	↓	↓	↓	↓	
Timolol	0	±	0	↓	↓	↓	↓	↓	
Isomer d propranolol	0	0	+ +	↔	↔	↓ ↔ ↓†	↓ ↔	↓ ↔ ↓†	+†

*Cardioselectivity of certain beta blockers is only seen with low therapeutic concentrations of drugs. With higher concentrations cardioselectivity [illegible] seen

†Effects of d propranolol occur with doses in humans well above the therapeutic level. The isomer also lacks beta blocking activity.

Table II Pharmacodynamic properties and some non-cardiac effects of β-adrenoreceptor drugs

Drug	*Cardio-selectivity**	*Partial agonist activity*	*Membrane stabilizing activity*	*Bronchoconstriction*	*Platelet aggregability*	*Plasma renin activity*	*Peripheral resistance*
Acebutolol	+	+	+	↑ ↔ ↓		↓ ↔	↑↔
Alprenolol	0	+ +	+	↑ ↔ ↓		↓ ↔	↑↔
Atenolol	+	0	0	↑ ↔ ↓		↓ ↔	↑↔
Metoprolol	+	0	±	↑ ↔ ↓		↓ ↔	↑↔
Oxprenolol	0	+ +	+	↑ ↔ ↓	↓	↓ ↔	↑↔
Pindolol	0	+ + +	+	↑ ↔ ↓	↓	↓ ↔	↑↔
Practolol	+	+ +	0	↑ ↔ ↓	↔	↓ ↔	↑↔
Propranolol	0	0	+ +	↑ ↔	↓	↓	↑
Sotalol	0	0	0	↑ ↔		↓	↑
Timolol	0	±	0	↑ ↔		↓	↑

*Cardioselectivity of certain beta blockers is only seen with low therapeutic concentrations of drugs. With higher concentrations cardioselectivity [illegible] seen

and blocks the orthostatic rise in plasma renin activity on standing. Dextro propranolol has no effect on renin release inhibited by racemic propranolol in the same patients, and has no effect on plasma renin activity in the rabbit. The suppressant effect of racemic propranolol is therefore dependent on the β-blocking action of the levoisomers.

The effect of the different β-blockers on resting and orthostatic renin release is variable. Among the non-selective blockers, propranolol causes the greatest reduction of both resting and orthostatic renin release; timolol causes significant reduction[12]; oxprenolol[13] and alprenolol have less effect (especially on orthostatic renin release); pindolol has the least effect (Weber and associates found that in the rabbit pindolol caused a rise in plasma renin activity; Stokes and colleagues[14, 15] found that patients switched from propranolol to pindolol continued to have good control of their blood pressure despite a rise in plasma renin activity). It has been suggested that the smaller effect of alprenolol, oxprenolol, and pindolol on renin compared with propranolol can be due to their partial agonist properties.

The cardioselective β-blockers show [illegible] variation in effect. practolol has no effect on renin[14]; metoprolol lowers resting and furosemide-induced renin release[11]; atenolol has conflicting reports. Amery and co-workers

showed no effect,[19] whereas Aberg[20] demonstrated a significant decrease in resting renin. Practolol's lack of renin effect may be related to its partial agonist activity. The effectiveness of the other two cardioselective β-blockers may suggest that at least in man, renin release is mediated by a β receptor. But other studies in experimental animals propose a β receptor for renin release and the question remains a matter of great controversy.

The crucial question, however, is whether there is a clinical correlation between the β blocker effect on reducing plasma renin activity and the lowering of blood pressure. Laragh's group[4] found that "high-renin" patients respond well to propranolol, "low renin" patients do not respond or may even show a rise in blood pressure, and "normal renin" patients have less predictable responses.

Castenfors and colleagues[13] also found a correlation between fall in plasma renin activity and fall in blood pressure using alprenolol. However other authors have been unable to confirm this relationship, either for propranolol or for other β-blockers.[14] Even in the "high renin" hypertensive subject, it has been suggested that renin may not be the only factor maintaining the high blood pressure. At present, the exact roles of renin and β-blockade causing and controlling hypertension remain to be more clearly elucidated.

4. Reduced plasma volume and venous return may be playing a role in the control of blood pressure by β-blockers. A few studies have shown these effects, both acutely and with long term therapy when heart failure was not present.[21] Since one would expect an impaired cardiac output to cause an increase in plasma volume, these early findings, though not yet fully investigated, are of great interest.

5. Peripheral resistance. Beta blockade has no primary action in lowering peripheral resistance and, indeed, may cause it to rise by unopposed alpha stimulation.[22] The vasodilating effect of catecholamines on skeletal muscle blood vessels is β_2 mediated, suggesting a possible advantage of cardiospecific β_1 blockers or drugs with partial agonist effects in therapy. However since cardioselectivity diminishes as the dosage is raised, and since hypertensive patients generally have to be given far larger doses than are required simply to block the β receptors, this cardioselectivity[24] is only relative and offers little if any real advantage.

6. Quinidine effect (membrane stabilizing). Some early investigative studies[23] indicated that the antihypertensive effect of propranolol paralleled the antihypertensive effect of quinidine, suggesting that the "membrane stabilizing" effect might be important. However later studies refuted these early findings.[25] All the beta blockers appear to reduce blood pressure, regardless of the presence of membrane effects.[14] This has been confirmed since d propranolol, with predominant "membrane" effects, does not affect blood pressure.

In summary, β blockers have been found to be useful in hypertension, although their precise mechanism of action remains unclear. Whether cardioselective beta blockers or agents with partial agonist activity will prove more or less advantageous compared with non-selective beta blocking drugs has yet to be determined.

Angina pectoris (Effects on heart rate and myocardial contractility—Table I). In 1948 Ahlquist[27] demonstrated that sympathetic innervation of the heart causes the release of norepinephrine which activates β-adrenoreceptors in myocardial cells. The effects of this stimulation cause an increase in heart rate, isometric force, and maximal velocity of muscle fiber shortening, leading to an increase in cardiac work and myocardial oxygen consumption.[28] The decrease in intraventricular pressure and volume caused by the sympathetic mediated enhancement of cardiac contractility tends, on the other hand, to reduce myocardial oxygen consumption by reducing myocardial wall tension (Law of Laplace).[29] Although there is a net increase in myocardial oxygen demand, this is normally balanced by an increase in coronary blood flow. Angina pectoris is felt to occur when oxygen demand exceeds supply, i.e., when coronary blood flow is restricted by coronary atherosclerosis. Since the conditions which precipitate anginal attacks (exercise, emotional stress, food, etc.) cause an increase in cardiac sympathetic activity it might be expected that blockade of cardiac β-adrenoreceptors [illegible] relieve the symptoms of the [illegible] is on this basis that the [illegible] β-blocking drugs in [illegible] studies have led to the [illegible] of one most important and [illegible] triumphs of the past [illegible]

Four main facto[illegible] systolic pressure, rate [illegible] pressure, and the size [illegible]

ute to the oxygen demand of the left ventricle. Of these, heart rate and systolic pressure appear to be the most important (heart rate × systolic blood pressure product is a reliable index to predict the precipitation of angina in a given patient).[11]

The reduction of heart rate effected by β-blockade has two important beneficial effects. (1) decrease in cardiac work, thereby reducing oxygen demand and, (2) the longer diastolic filling time associated with slower heart rate allows for greater coronary perfusion time. β-blockade also reduces exercise-induced blood pressure rise, velocity of cardiac contraction and oxygen consumption at any work load.[12]

Studies in dogs have shown that propranolol caused a decrease in coronary blood flow.[13] However subsequent work in dogs demonstrated shunting within the coronary circulation with β-blockade in a manner that maintains blood flow to ischemic areas, especially in the subendocardial region.[14] Simultaneous with the decrease in myocardial oxygen consumption in man β-blockade has also been found to cause a reduction in coronary blood flow and a rise in coronary vascular resistance.[15] However the over all decrease in oxygen consumption by the heart as a whole may be sufficient cause for the decrease in coronary blood flow.

Virtually all β-blockers, whether or not they have partial agonist activity membrane stabilizing activity general or selective β-blocking properties, produce some degree of increased work capacity without pain. Therefore, it must be concluded that this results from their common characteristic blockade of cardiac beta receptors.[15] For example, both d and l propranolol have membrane stabilizing activity but only l-propranolol has significant β-blocking activity. The racemic mixture (d and l-propranolol) causes a decrease in heart rate and force of contraction in dogs, while the d isomer has hardly any effect.[16] In man, d propranolol, which has membrane[17] but no β-blocking properties, has been found to be ineffective in angina pectoris using very high doses. The same type of ineffectiveness has been demonstrated by d alprenolol as well.[18]

The effect of β-blocking drugs in acute exercise in angina pectoris is of interest. Although exercise tolerance improves (the increment in heart rate and blood pressure with exercise is blunted) the pressure rate product (systolic blood pressure × heart rate) achieved when pain occurs is less than that reached during a control run. The depressed pressure-rate product at the onset of pain (about 20 per cent reduction from control) occurred with various intravenously administered β-blocking drugs that differed in certain properties propranolol (membrane stabilizing activity), oxprenolol (membrane stabilizing and intrinsic sympathomimetic activity) practolol (cardioselective blockade and intrinsic sympathomimetic activity) and sotalol (minimal membrane stabilizing activity).[19] Thus, although there is increased exercise tolerance with β-blockade, patients exercise less than might be expected. This probably represents the potentially adverse effect of β-blockers in increasing left ventricular size, causing increased left ventricular wall tension and increased oxygen consumption at a given blood pressure.[20]

All beta blockers will limit the heart rate increment with exercise however they cause differing effects on the resting heart rate. Propranolol and metoprolol slow the resting pulse more than oxprenolol, pindolol, and practolol; d-propranolol had very little resting pulse slowing activity. Morgan and associates[21] also found a differential pulse slowing activity among four β-blockers they tested. propranolol and timolol reduced pulse rate more than pindolol and alprenolol. It would appear that β-blockers lacking partial agonist activity slow the resting pulse rate more than the β-blockers that have partial agonist activity.

A possible explanation why drugs with intrinsic sympathomimetic activity do not affect the resting heart rate to the same degree as they affect the increment in heart rate with exercise probably relates to the increased sympathetic tone with exercise. At rest, without a high degree of sympathetic activity the intrinsic sympathomimetic effect may be more apparent than the β-blocking effect, the converse being true with exercise.

The therapeutic benefit of β-blockade in angina pectoris is now established beyond question. There are many double-blind studies demonstrating a significant reduction in the frequency of anginal attacks. Improvement is dose-related and dosage must be titrated for each individual patient. All the various β-blockers, despite their differing characteristics and activities, have equal effect in the relief of angina.

Propranolol is the most widely used β blocker today It is non-selective, has membrane stabiliz ing activity but has no intrinsic sympathomimet ic activity There have been numerous trials of propranolol, using fixed single and multiple dose level trials, that have shown its efficacy in angina pectoris in a dose-related manner[41] Alprenolol and oxprenolol, which appeared soon after propranolol was introduced, are like propranolol, non-selective β-blockers with membrane stabiliz ing activity and good antianginal effects. Unlike propranolol, they both possess intrinsic sympa thomimetic activity Although trial studies for the most part have shown beneficial effects from both drugs, the presence or absence of a dose-response relationship for alprenolol has not been firmly established.

Sotalol is a non-selective β-blocker with neither intrinsic sympathomimetic activity nor any membrane stabilizing activity In an acute intra venous study Prichard and co-workers found it equivalent to propranolol and minimally superior to oxprenolol in delaying the onset of pain. However, in a longer oral dose study Horn and Prichard found propranolol to be more effective Other studies[42, 43] have shown the two drugs to be roughly equivalent. Timolol, another non-selec tive β-blocker with neither intrinsic sympathomi metic activity nor "membrane effect," was shown in a large multicenter trial to be effective in reducing the frequency of anginal attacks.

Non-selective beta blockers are contraindi cated in patients with obstructive airway disease. The development of *selective β blockers*, there-fore, has had important therapeutic implications (although cardioselectivity is not absolute and decreases with increasing dose) Practolol, which has intrinsic sympathomimetic activity and cardioselectivity was the first of these agents and, while in use, was found to be effective, though less so than propranolol in equivalent doses.[47] However with increased reports of serious toxic effects (SLE type syndrome, eye lesions, skin lesions, sclerosing peritonitis) the drug was withdrawn. Recently other selective β-blockers have been developed.

Atenolol differs from practolol in that it lacks intrinsic sympathomimetic activity In an acute study comparing atenolol with propranolol in severe angina, both drugs produced an equal reduction in exercise-induced tachycardia, but atenolol produced a higher maximal working capacity than propranolol.[48] This increased work capacity may reflect the lack of interference by atenolol on the peripheral vascular adaptation to exercise. Roy and colleagues,[49] in comparing atenolol with placebo found that it significantly reduced the number of nitroglycerin tablets consumed and the frequency of angina attacks.

Metoprolol is another selective β-blocker devoid of intrinsic sympathomimetic activity whose preliminary data indicate its effectiveness in angina.[50]

In summary all beta-blockers, despite their differing pharmacodynamic properties, are effec tive in angina pectoris, blunting the heart rate-blood pressure-contractility increments in exercise. This enables patients to do more work at lower oxygen demands, despite increments in end-diastolic volume and myocardial wall ten-sion. Whether or not drugs with intrinsic sympa thomimetic activity (e.g., pindolol) will prove safer than propranolol due to the potential lessening of myocardial depression is yet to be determined (This will be discussed in a future article)

Arrhythmias (Table I) Although beta blocking drugs have been used for treating cardiac arrhythmias for over a decade, their precise mode of action remains unclear Two main effects of these drugs, β-blockade and membrane stabilizing activity have been identified.

1 *β-blockade*. By blocking adrenergic stimula tion of cardiac pacemaker potentials, β-blocking drugs are useful in controlling arrhythmias that are caused by enhanced automaticity and re-entry In concentrations which cause significant inhibition of cardiac adrenergic receptors, the slope of the packmaker action potential (either sinus or ectopic) is reduced, particularly in the presence of catecholamines or ouabain.[51] Thus, arrhythmias related to sympathetic hyperactivity would be expected to respond to β-blockade Similarly in myocardial infarction, where there are increased levels of circulating catecholamines causing enhanced automaticity β-blockers are likely to be useful.[52] This is not to say however that beta blockers will *only* be effective in arrhythmias directly related to catecholamines (e.g., pheochromocytoma, halothane anesthesia) Clinically their usefulness has been demon strated in many other types of arrhythmias as well. Their beneficial effect in these situations probably derives from removal of normal adrener

gic effects that may be unfavorably additive to the *major* arrhythmia-causing stimulus. One such example would be arrhythmias related to digitalis toxicity

2. *Membrane stabilizing action.* The second possible mechanism explaining the antiarrhythmic effect of β-blocking drugs is their membrane stabilizing or depressing action, often referred to as the "quinidine-like" or local anesthetic" action. This property is unrelated to inhibition of the action of catecholamines, and is held to an equal extent by both the d and l isomers of the drugs (d isomers have virtually no beta blocking activity). It is characterized by a reduction in the rate of rise of the intracardiac action potential without affecting the duration of the spike or the resting potential. The effect has been explained by an inhibition of the depolarizing inward sodium current.

It should be noted, however that in *in vitro* experiments with human ventricular muscle the concentration of propranolol required to produce this effect is 50 to 100 times the concentration generally associated with inhibition of exercise induced tachycardia. The concentrations of propranolol needed to produce this effect are in the *milli* molar range, whereas general clinically used doses produce *micro*-molar concentrations, at which level only beta blocking effects occur

It seems probable, therefore, that in usual therapeutic doses the main factor in the antiarrhythmic effect of these drugs is β blockade. Coltart and associates and Shand have shown that arrhythmias are suppressed by plasma propranolol concentrations 1/50th to 1/100th of the level needed for membrane stabilizing action Jewitt and Singh have observed that d propranolol, which possesses membrane stabilizing properties but no beta blocking action is weak as an antiarrhythmic even in very high doses. Practolol, on the other hand, is clinically effective as an antiarrhythmic although it lacks membrane stabilizing characteristics

If β-blockade is, indeed, the major mechanism for antiarrhythmic effect, and the clinical relevance of membrane stabilizing properties is negligible then one would expect *all* β blockers to have similar antiarrhythmic effect for a comparable degree of β-blockade This, in fact, appears to be the case. No superiority of one β blocking agent over another in the treatment of arrhythmias has yet been demonstrated Any differences in their over-all clinical effects must, therefore, be assumed to be related to their other associated pharmacological properties.

Effects on the sinus node and atrioventricular conduction In animals and in man, β-blockers slow the rate of discharge of the sinus and ectopic pacemakers and increase the functional refractory period of the atrioventricular (A V) node. They also slow both antegrade and retrograde conduction in anomalous pathways.

Since all β blockers studied so far cause an increase in atrioventricular conduction time, advancing A V block is a potential complication when β-blockers are used. From both animal and human studies, it is apparent that those β-blockers like propranolol, which do not possess intrinsic sympathomimetic activity but have potent membrane stabilizing properties, cause the greatest increase in atrioventricular conduction time. In contrast, Giudicelli and co-workers showed the partial agonist activity (intrinsic symp mimetic activity) of pindolol, practolol, an prenolol provides protection from the conduction impairment induced by β-blocka

It should also be noted that β-blocking d can, in large doses, induce sinus node dysfunc that may lead to sinus arrest or sinoatrial bl β-blocking drugs, therefore are best avoide patients with sick sinus syndrome, which c potentially be aggravated by beta blockade.

Vascular resistance and peripheral blood f (Table II) Isoproterenol mediates its effects cardiac contractility through the beta-1 recep and its peripheral vasodilatory effects thro the beta 2 receptor Propranolol, by block both receptors, leaves uninhibited the alp adrenergic tone in the periphery This would te to increase peripheral vascular resistance, effect which has been clearly demonstrated w propranolol. This increase in periphe resistance might potentiate the rate lower effect of propranolol and negate some of antihypertensive properties. This increase peripheral resistance can affect blood flow in th limbs, coronary arteries, renal circulation, splanchnic vessels, and in the brain. Drug with beta 1 cardioselectivity (e.g., practolol) hav little or no effect on peripheral vessels (in dose where the drugs are cardioselective) and tend therefore not to increase peripheral resistance Drugs with intrinsic sympathomimetic activit (e g pindolol) do not raise peripheral resistance as much as propranolol

Inhibition of peripheral vasodilation probably

is the mechanism of the beneficial effect of propranolol in migraine.[illegible] Pindolol and alprenolol, perhaps because of their partial agonist activity have shown little or no effect in the treatment of patients with migraine.

Non-cardiovascular effects

Oxygen transport (effects on the oxyhemoglobin dissociation curve) Altered oxyhemoglobin dissociation could facilitate oxygen availability to poorly perfused zones of myocardium in patients with ischemic heart disease.

It was suggested that the oxyhemoglobin dissociation curve could be affected by administration of beta blocking drugs. Oski, Miller and de Livoria[illegible] showed that propranolol produced a favorable alteration of the curve to the right in normal subjects, probably by a release of membrane bound 2,3 diphosphoglycerate (2,3 DPG) These results were not confirmed by Brain and associates,[illegible] who found no significant change in p50 (pO_2 at 50 per cent hemoglobin saturation) using a higher oral dose of propranolol, and no alteration in erythrocyte 2,3 DPG We also were not able to corroborate the findings of Oski and colleagues regarding changes in p50 and 2,3 DPG (during rest and with exercise) in patients with angina pectoris treated with propranolol or pindolol.[illegible]

Although other beta-blockers have not yet been well investigated, it seems that the effects of beta-blockers on the oxygen dissociation curve and on O_2 delivery are negligible.

Effects on the bronchial tree (Table II) Bronchodilation is mediated through catecholamine stimulation of the β_2 receptors in the lung. Propranolol, which blocks beta receptors (β_1 and β_2) can precipitate bronchospasm in some patients.

All beta-blocking drugs, including those with cardioselectivity and partial agonist activity can induce bronchoconstriction in patients with asthma and bronchitis. Comparative studies have shown, however that compounds with partial agonist activity (alprenolol, pindolol, practolol) and cardioselectivity (practolol, metoprolol)[illegible] are less likely to increase airway resistance (as measured by forced expiratory volume in one second (FEV_1) in asthmatic subjects than propranolol. Nevertheless, practolol,[illegible] despite cardioselectivity and partial agonist activity can induce bronchospasm in susceptible individuals.[illegible] Patients who develop asthma while taking a cardioselective β-blocker will respond readily with bronchodilation from standard doses of β_2 stimulant drugs such as Salbutamol, whereas patients taking a non-selective β-blocker like propranolol will not.

Effects of beta-adrenergic blocking agents on metabolism Hypoglycemia has been reported as a side effect of non-selective β-blockade in diabetic subjects on insulin.[illegible] The severity of this insulin-induced hypoglycemia may be lessened with cardioselective β-blockers.[illegible] The symptoms of hypoglycemia are also modified by propranolol, but sweating is enhanced.[illegible]

Epinephrine in man stimulates glycolysis in skeletal muscle predominantly via beta-adrenoceptors and in the liver predominantly via alpha adrenoceptors.[illegible] In normal subjects, abolition of glucose mobilization requires simultaneous blockade of alpha-adrenergic receptors in the liver and beta adrenergic receptors in skeletal muscle with phenoxybenzamine and propranolol, respectively.[illegible] Resting plasma glucose and insulin concentrations in normal individuals are not affected by propranolol. The fall of plasma glucose levels after administration of insulin is also unaffected. However the rate of return to normal of blood glucose levels after insulin induced hypoglycemia is reduced and the increase of plasma glycerol is prevented. These effects depend in part on the beta adrenergic effect of catecholamines reflexly released in response to the hypoglycemia. For this reason, in diabetic patients treated with insulin, and in some other situations (e.g., fasting) beta blockade with propranolol may be associated with hypoglycemia.[illegible]

In contrast, propranolol has been reported to precipitate hyperglycemia and hyperosmolar non ketotic coma and to prevent recurrent hypoglycemia in a patient with insulinoma.[illegible]

These contrasting effects result from an interplay of several factors gluconeogenesis, liver and skeletal muscle glycogenolysis, peripheral glucose utilization, and growth hormone, glucagon, and insulin secretion. β-blockers inhibit glucose-sulfonylurea-stimulated insulin secretion. There is good evidence that the β-receptor for insulin secretion is of the β_2 type.[illegible]

Administration of propranolol has been shown to reduce plasma free fatty acid levels at rest, after prolonged fasting, and during exercise, emotion, or insulin induced hypoglycemia.[illegible] Also, propranolol, but not practolol, blocks the lipolytic activity of isoproterenol.[illegible] The in

crease in free fatty acids occurring during epinephrine infusion is blocked by propranolol, but accentuated by phentolamine, suggesting the presence of an additional inhibitory α adrenergic mechanism. The lipolytic activity of epinephrine can also be blocked by practolol, but only at doses significantly higher than those affecting its cardiovascular manifestations. Thus, although the receptor sites associated with adrenergic stimulation of lipolysis fulfill many of the characteristics of a β-receptor the presence of an inhibitory effect that can be reversed by phentolamine, and a reduced sensitivity to practolol show that they are not identical with those affecting heart rate and force of contraction

Although the metabolic effects of beta blockade are not nearly as prominent as their hemodynamic effects, and the incidence of metabolic side effects is low beta adrenergic blocking agents should be used with caution in patients prone to hypoglycemia, particularly insulin treated diabetic subjects. Cardioselective blockers, (e.g., metoprolol, acebutolol) or drugs with intrinsic sympathomimetic activity (e.g., pindolol) may not interfere as much with the physiologic compensations for insulin induced hypoglycemia.

Effects on blood coagulation (Table II) Adrenergic stimuli may interact with the hemostatic processes at several points. Exercise or epinephrine administration causes a rapid rise in Factor VIII (anti hemophilic globulin) levels, which can reach two to four times control level. This increase can be totally blocked by propranolol or alprenolol but not by phenoxybenzamine or practolol.

Propranolol has been shown to interfere with exercise-induced increments in fibrinolytic activity whereas practolol has no effect.

In contrast to this potential detrimental effect on fibrinolysis, some beta blockers have a potential beneficial effect on platelet activity Excessive reactivity of blood platelets may contribute to arteriosclerotic vascular disease and its complications. The platelets of patients with thrombotic vascular disease show increased turnover rates and augmented responses to a variety of aggregating agents. We have observed that the platelets of patients with angina pectoris have exaggerated aggregation responses which become normal during propranolol therapy

In *in vitro* experiments, propranolol (in concentrations similar to those safely achieved *in vivo*) abolished the second wave of human platelet aggregation induced by ADP and epinephrine and inhibited aggregation induced by collagen and thrombin

Propranolol blocked the release of ^{14}C-serotonin from platelets, inhibited platelet adhesion to collagen, and interfered with clot retraction. Inhibition appeared unrelated to beta adrenergic blockade as d (+) propranolol (which lacks beta-blocking activity) was equipotent with l (–) propranolol. Moreover practolol, a beta-blocking drug which is not membrane active (non lipophilic) did not inhibit platelet function. These studies suggested that propranolol, like local anesthetics, decreases platelet responsiveness by a direct action on the platelet membrane. Modulation of platelet function by propranolol may occur at concentrations achieved with usual clinical doses of the drug.

Oxprenolol and pindolol (drugs with membrane activity) have also been shown to reduce platelet aggregability though to a lesser degree than propranolol. If platelet hyperaggregability is contributory in atherosclerosis and its complications, beta blockers, with effects on platelet membranes, may provide an extra protec effect in patients.

Recently heightened platelet hyperaggreg ity has been described in patients with an pectoris who had abrupt withdrawal of chr propranolol therapy Whether or not pla hyper responsiveness contributes to the "rebo phenomenon described with beta blocker w drawal is provocative and warrants further i tigation.

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Annotations

Statistical support for or against transplantation

For a number of years current statistics have shown that patients on home dialysis do best, patients in hospitals receiving dialysis survive less well, and transplanted patients fare even worse. So transplantation would seem to be a life-shortening procedure and we should ask ourselves whether we are right in putting our patients on the receiving list. Actually home dialysis has been proposed as a first choice and some ha en suggested stopping transplantation altogether. In fact the number of cadaver grafts in Europe rose from under 606 in 1969 to 2,117 in 1976. In spite of untoward statistics 12,252 transplantations of cadaver kidneys have been performed up to the end of 1976. While statistical support seemed absent, various other constructions have been used to justify continued transplantation. For instance, one such attitude had it that the transplanted patient would live shorter yet better than his dialysed counterpart. This is not only doubtful philosophy but also wishful thinking, since transplanted patients who die early often do so after following a poor postoperative course.

Yet there is better support for the continued effort in transplantation since current statistics are based on faulty premises. With a few exceptions, available statistics compare as alternatives different forms of treatment—dialysis versus transplantation—which essentially they are not. In the prevailing shortage of donor organs, it is impossible to provide all patients in end-stage renal failure with a transplant. When the creatinine clearance falls below 3.0 ml/minute, the patient has to be dialysed. Live donor recipients only have a choice between dialysis and transplantation at the outset of treatment. More likely a patient will be offered transplantation after being established on dialysis. As soon as a cadaver organ is available (average waiting time 22 months), he may be transplanted. Within 12 months about 60 per cent of transplanted patients go back to dialysis from which they may

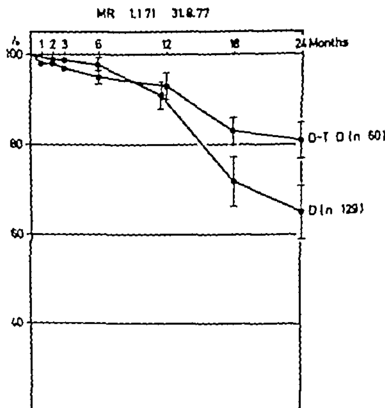


Fig. 1 Cumulative survival rates on combined management (*D-T-D*) and on dialysis treatment alone (*D*). Comparing the real alternatives the Marburg patients under combined management (*D-T-D*) did significantly better than on dialysis treatment alone (*D*).

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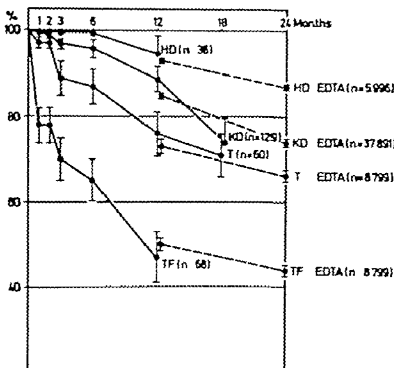


Fig. 2. Cumulative survival rates of patients on home dialysis (*HD*), hospital dialysis (*KD*), and after transplantation (*T*), as well as graft survival rates (*TF*) in Europe and Marburg (*MR*) are shown. By conventional presentation, the Marburg results after 12 and 18 months are comparable with those of the European material.

be transplanted again. The remaining patients continue on dialysis for medical reasons or because no suitable organ has been available. So the real choice in current management of end-stage renal failure is between combined treatment with dialysis and transplantation (D-T D) or dialysis treatment alone (D).

Set against patients who are maintained on dialysis alone (D) without being offered transplantation, it will be seen whether the inclusion of transplantation (D-T D) does improve cumulated survival in end-stage renal failure. Group D included all patients as long as they were treated in home or limited dialysis in care centers. Upon transplantation, the recipient of a renal graft left group D and was transferred to group D-T D. Group D-T D consisted only of patients who had been transplanted at some stage and included those who had both previous and subsequently survived on dialysis. Available data have been analyzed by the implementation of the life table method which is in current use with the E D T A Registry. As can be seen from Fig 1 the survival rate under combined management (D T D) is significantly better than with dialysis alone.

Conventional analysis of our data is shown in Fig 2. There is no significant difference between local results and the European average. Presentations along these lines are valuable and should be continued for the purpose of comparison between different centers. But for a rational evaluation of different regimens in the management of chronic renal failure, the statistical approach suggested above should be adopted.

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Does DC cardioversion affect isoenzyme recognition of myocardial infarction?

Determination of serum concentrations of the enzymes creatine kinase (CK) and lactic dehydrogenase (LDH) and more importantly their cardiac isoenzymes CK_{MB} and LDH_1 has been extremely useful in establishing or confirming the diagnosis of acute myocardial infarction.[1-4] In appropriate clinical settings, elevated serum levels of these enzymes, and their myocardial fractions in particular is believed to specifically indicate acute myocardial necrosis. Since acute myocardial necrosis is often accompanied by cardiac arrhythmias and since direct current (DC) cardioversion is frequently used in the therapy of cardiac arrhythmias, it is important to know whether DC cardioversion, too, can elevate CK (total and MB) or LDH (total or fraction 1). If so, the use of DC cardioversion would invalidate the use of these serum enzyme determinations in establishing the diagnosis of acute myocardial infarction in patients whose arrhythmias have been treated with DC countershock. Although this question was answered in part by Ehsani and co-workers, who showed that high energy level DC cardioversion may elevate total CK values moderately and the CK_{MB} fraction infrequently and mildly its effects on LDH values were not evaluated.

To provide initial data on the effect of DC cardioversion on serum LDH (total and fraction 1) and to provide additional data on the effect of DC cardioversion on serum CK (total and MB) we determined serum concentrations of total CK, total LDH, CK_{MB} and LDH_1 serially in 18 patients without clinical or electrocardiographic evidence of acute cardiac ischemia who underwent elective DC cardioversion for nonacute atrial arrhythmias. Utilizing our previously reported technique, serum enzyme concentrations were determined five minutes before, within five minutes after and at 6, 12, and 24 hours after DC cardioversion. In the first nine patients isoenzyme fractionation was performed on all samples; in the remaining patients isoenzyme fractionation was performed on all samples where total CK or LDH were elevated. As detailed elsewhere, 11 patients achieved cardioversion with one or two shocks and less than 100 cumulative Watt seconds (W-sec) per patient. In five patients cardioversion was achieved with one to three shocks and 100 to 250 cumulative W-sec per patient. Two patients required a total of 600 W-sec each, one received two and the other five shocks in total. The resulting serum enzyme determinations in these 18 patients are summarized in Table I.

Following cardioversion new elevations of total CK developed in one patient and were evident at six, 12, and 24 hours. CK_{MB} was absent. This patient received two shocks totaling 600 W-sec. Following cardioversion new elevations of total LDH developed in four patients, each of whom received be[illegible] 30 to 125 W-sec. In all four enzyme elevation was present either immediately after cardioversion or at six hours, and the elevation persisted at 12 and 24 hours. LDH_1 was absent in each case. There were no hemodynamic nor arrhythmic complications in these five patients.

Our findings, like those of Ehsani and associates, sugg[illegible] that DC cardioversion may occasionally elevate total C[illegible] most probably when high energies are used. However, CK_{MB} elevations are unlikely to occur. Although LDH elevations appear to occur slightly more frequently than total C[illegible] elevations following cardioversion and with lower deliver[illegible] energies, like CK_{MB} the myocardial fraction (LDH_1) does n[illegible] appear to rise. Thus, our results suggest that DC cardioversion should not interfere with the specificity of serum CK_{MB} a[illegible]

Table I Cardioversion enzyme data

Any enzyme elevation before cardioversion		New enzyme elevations after cardioversion				Total number of patients
		Immediately after	at 6 hours	at 12 hours	at 24 hours	
Total CK	2/18	0/18	1/18	1/18	1/18	1/18
Total LDH	4/18	3/18	3/18	1/18	1/18	4/18
CK_{MB}	Zero	Zero	Zero	Zero	Zero	Zero
LDH_1	Zero	Zero	Zero	Zero	Zero	Zero

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LDH, ele tion is indicating the presence of ischemic damage associated with the treated arrhythmia, particularly hen these t o isoenzyme determinations are pplied in combina tion.

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Effect of reduction in salt intake on hypertension

Hypertension is a major health problem of this generation. Comparativ data on the change in its incidence is not available, but probably 15 per cent of the adult population has diastolic blood pressure greater than 95 mm. Hg and in older age groups this percentage may reach 40 per cen This level of blood pressure is associated with increased morbidit and mortality Why the prevalence of hypertension has increased is unknown. It may be due to improvement in diagnosis and an appreciation that mild elevation of blood pressure has harmful effect. At present, programs are under way to detect patients with mild elevation of blood pressure and control the blood pressure with drug therapy to determine if long-term treatment of mild hypertension reduces morbidity and mortality If proven to be of benefit, treatment of 15 per cent of the population will use an excessi amount of medical manpower and financial resources. The question is also raised whether side-effects of the medication used, even though they have low morbidity and mortality may exceed the benefit to be gained. It must be emphasized that this refers to mild hypertension, as there is no doubt that treatment of more severe degrees of hypertension is justified economically and medically

An association between sodium and hypertension has been postulated for long time Epidemiologically the relationship between sodium intake and hypertension is strong and this linkage is strong enough to suggest causal role for salt in the genesis of many cases of hypertension This linkage has been shown hen comparing the incidence of hypertension in one community compared with another It has been less clearly shown inside single population, though in genetically similar people it does exist. Most studies hav not show correlation between an individual salt intake and hypertension, but there is no need for this relationship to be shown as it is likely that if group of people had the same high salt intake then only those individuals who have a genetic predisposition causing poor excretion of salt become hypertensive. Thus hen comparing individual people, sodium intake of 400 mmol./day will not cause hypertension in every person, but only in those who have genetic or acquired defect in their ability to handle sodium. However, recent study showed relationship.

What is not clear is the role of salt restriction in the treatment of hypertension. Severe salt restriction (to an intake of less than 10 mmol./day) significantly reduces blood pressure and improves the prognosis in people with severe or malignant hypertension. This degree of salt restriction is not palatable to most people and compliance with such regimen is low In other situations, salt restriction does improve the control of hypertension. The effect of diuretic drugs can be reversed if a person is given high sodium intake. Sodium restriction improves the control of hypertension in people on other antihypertensive drug medication. The real question is not "Is it possible to treat an individual person by sodium restriction, but Is it possible by reducing the sodium intake of the community to reduce the incidence of hypertension?" A procedure such as this which could utilize public health control measures would have greater likelihood of success than procedures using drug therapy and it would be economically feasible. The following suggests that this is possible. Parijs and colleagues[?] have shown in a double-blind crossover study of mild hypertension that reduction of sodium chloride intake did reduce blood pressure. The study had crossover periods of one month duration and longer period of therapy may have reduced blood pressure more. In more recent study which was designed to study the effect of therapy on long term prognosis of hypertension, Morgan and associates[?]

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Table I 24 hour urinary sodium excretion in patients given dietary advice

	Urinary sodium				
	Mean	<100 mmol./day	<150 mmol./day	>200 mmol./day	>300 mmol./day
Before	191 ± 8	11%	29%	37%	6%
After	157 ± 7	28%	62%	24%	3%

placed 30 male patients on a reduced salt diet. The people in this study were all male, mean age 56, with a diastolic blood pressure between 95 and 110 mm. Hg. They were divided into four groups. One group was treated as a control group. The second group was given dietary advice which if followed fully could have reduced their sodium intake to 70 to 100 mmol. salt/day. The third group was treated with a thiazide diuretic followed by Aldomet and fourth group was treated by a beta blocker followed by a thiazide diuretic. The mean sodium intake of each group was similar before the study started and the distribution pattern showed some people with a very high sodium intake. In patients treated with sodium restriction the full aim was not achieved, but there was a significant reduction in sodium excretion from 195 to 157 mmol./day. Of more significance was the change in the distribution pattern (Table I). Whereas in the initial collections 37 per cent of the urinary sodiums were above 200 mmol/day this only occurred in 24 per cent of the urines after dietary advice was given. Thus the percentage of patients with very high salt intake was reduced significantly. There was a fall in mean blood pressure of 7.5 Hg which was greater than the change in controls but less the fall in patients treated with drugs. In the study which reported in the Lancet, it is possible that more effective control of salt intake may have reduced the blood pressure even further.

Sodium restriction is not being advanced as the sole therapy for established hypertension (that is, diastolic blood pressure greater than 110 mm. Hg) but the study showed that a significant lowering of blood pressure is able to be achieved if salt intake is reduced. Compliance with such a regimen may be poor and needs to be verified by 24 hour urinary sodium collections before the therapy is discarded.

The results also showed that it was possible to modify the patient dietary intake by relatively simple educational instructions given on a one-to-one basis by doctor to the patient. In certain individual cases this was reinforced by advice from a dietician. The pattern of urinary sodium excretion showed that initially sodium intake as reduced but patients tended to relapse back towards their higher intake. This emphasizes the importance of continuing education of these patients regarding salt restriction. If the success of a small study of this nature could be extended to a larger scale we may have a chance of reducing the epidemic of hypertension in the western world. The main problem will be, however, to devise methods by which such a dietary change in the population can be implemented.

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Of acute anginal discomfort and tachycardia

Not infrequently patients with coronary [illegible] disease will suddenly develop a tach[illegible] [illegible] ventricular response. In [illegible] few seconds or minutes the patient [illegible] seized with a typical episode of severe angina pectoris with all the associated symptoms and manifestations [illegible] of myocardial infarction. If the rapid ventricular rate continues, the syndrome will also continue in spite of the sublingual use of one or more tablets of nitroglycerin. The patient, family, and even his physician will think he is developing [illegible] infarct or "heart attack." He is usually rushed to the hospital

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at emergency room and CCU etc., but when the ventricular tachycardia disappears minutes or hours later the symptoms and signs suddenly disappear. The objective manifestations of myocardial infarction, such as an increase in erythrocyte sedimentation rate, fever etc., do not develop. The enzyme levels in the serum increase only slightly or not at all, and the electrocardiogram may or may not reveal changes of angina pectoris but will not show those of myocardial infarction.

Meticulous and detailed history taking will reveal the sequence of events during the episode. The mechanism is most likely due to the rapid rate and high power output of the ventricles in which the volume rate of coronary blood flow is restricted by the organic obstructive coronary artery disease while the myocardium continues to work vigorously and extensively. The ventricles are "driven so hard" by the tachycardia that an acute relative or "functional" ischemia of the myocardium results, followed by the clinical manifestations of infarction. Nitroglycerin does not arrest the tachycardia, but the manifestations rapidly and dramatically subside when the normal resting heart rate is restored and the need of the myocardium for blood is reduced to a level possible to attain through the narrowed, diseased coronary arteries.

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Letters to the Editor

Myoglobinuria and rhabdomyolysis

To the Editor:

Myoglobinuria and non-traumatic rhabdomyolysis have recently been described in a case of status asthmaticus. Vigorous contractions of the respiratory muscles (intercostal, diaphragmatic, and accessory) during an asthmatic attack are equivalent to severe exercise. Repeated coughing adds to the severity of the myoglobinuria. Proper hydration can prevent acute renal failure.

Secondly, I would also anticipate a rise in SMb during hypothermia, with or without a shivering component. Carlson and Rapaport have shown that CPK MB, the cardiac fraction of CPK, is elevated in hypothermia without evidence for acute myocardial damage.

These reports should further highlight the non-specificity of SMb elevations.

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New physical sign during myocardial ischemia—limb venous engorgement, nine cases

To the Editor:

We would like to report briefly on nine patients with limb venous engorgement in association with angina pectoris.

Eight of nine patients with symptoms characteristic of angina pectoris also reported simultaneous engorgement and discomfort of limb veins associated only with angina. The other case had venous engorgement both with and without angina. Venous swelling immediately followed the onset of chest and arm discomfort in eight cases and preceded it in one. The veins were described independently by patients and several family members as being markedly swollen, rigid, and painful with an estimated diameter of six millimeters during and two millimeters after an attack. During very severe episodes, simultaneous recurrent ache occurring along the entire length of the left greater saphenous vein was described by one patient. Vein discomfort, swelling and angina were always promptly relieved by rest and nitrates. Coronary artery angiography revealed severe disease of at least one vessel in all nine cases. The venous engorgement and angina abated in nearly all patients, either on the maximum medical therapy or following coronary artery bypass surgery. A characteristic episode now occurs as frequently as once a [illegible] for a period of one minute relieved by nitroglycerin [illegible] infrequently as greater than one year between attacks. Because of its rarity and brevity, measurements of the phenomenon have been unsuccessful to date.

None of the patients has had venous engorgement prior to the onset of angina pectoris. Normal coronaries were observed in an additional patient who also described rare episodes of limb venous engorgement relieved by nitroglycerin.

We have been unable to find a prior description of this phenomenon.[1-6]

Additional observations and acquisition of data will be necessary before the mechanism of action can be determined. Because of the tenseness and rigidity of the veins with [illegible] it is possible that there is selective spasm of certain [illegible] associated with the ischemia.[6-8]

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Spontaneous variability in arrhythmia frequency

To the Editor:

Dr. Orr and co-workers, in their letter "Physiological sleep patterns and cardiac arrhythmias" (Am. Heart J. 97:128, January 1979) conclude that such considerable spontaneous variability in arrhythmia frequency occurs from one monitoring period to another that the clinician must be cautious in interpreting the results of limited monitoring. We and our colleagues[1] recently reported the results of extensive (three consecutive 24-hour) monitoring studies performed in 15 clinically stable patients with various cardiac disorders and frequent ventricular ectopy and documented the extent of this variability. Using an analysis of variance we demonstrated that even in otherwise stable individual patients one may expect to see as much as 90 per cent change in mean hourly ectopic frequency from one 8-hour period to another and more than 80 per cent change in frequency in comparing consecutive 24-hour periods. Thus, we concur in both our findings and conclusions.

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Carotid sinus hypersensitivity—asystole and hypotension in the same patient

To the Editor:

Carotid sinus hypersensitivity has been defined as cardiac asystole lasting at least three seconds, or a fall in blood pressure of 50 mm. Hg or more, in response to carotid sinus massage. Syncope may result from either mechanism, and both phenomena may be present in the same patient, although hypotension might be masked by precedent asystole. The patient described here illustrates this dual mechanism—the insertion of a cardiac demand pacemaker preventing asystole but not the hypotension induced by carotid sinus massage.

B. R. was an elderly man who fainted in an elevator sustaining a fractured skull. Little was done diagnostically until a second episode of syncope prompted carotid sinus massage which resulted in prolonged cardiac asystole. A cardiac demand pacemaker was implanted and subsequent carotid sinus massage induced a fall in blood pressure from 170/80 mm. Hg to 80/50 mm. Hg associated with severe lightheadedness without cardiac asystole.

This patient manifested both hypotension and cardiac asystole caused by carotid sinus hypersensitivity, hypotension becoming apparent only after pacemaker insertion prevented cardiac asystole. It follows that any patient with carotid sinus hypersensitivity who has a cardiac pacemaker implanted for asystole should have carotid sinus massage to ascertain blood pressure response, because subsequent syncope, lightheadedness, or weak spells may be due to hypotension rather than to pacemaker failure, thereby obviating empirical changing of the pacemaker.

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Nitroglycerin and blood oxygen dissociation curve of normal subjects

To the Editor:

Several drugs induce a shift of the oxyhemoglobin dissociation curve (ODC). The action of nitroglycerin on the ODC is controversial. Nitroglycerin (GTN) added to a solution of hemoglobin, administered sublingually to normal volunteers, or added to the blood of isolated canine heart preparations[1] fails to change significantly the P_{50}. On the contrary intracoronary infusion of GTN in isolated dog heart preparations increases significantly coronary venous PO and P_{50}.

To our knowledge the effect of GTN on the whole ODC has never been assessed. The purpose of our work is to establish whether or not high dosage of GTN influences the ODC of healthy normal subjects.

Nitroglycerin was administered sublingually (2.0 mg.) to seven normal subjects (two females) aged from 22 to 42 years. Arterial blood was sampled for the determination of blood gases, hematocrit, hemoglobin concentration, 2,3-DPG and ODC, before and 20 and 60 minutes after intake of GTN.

Blood gases were determined by a conventional analyzer (Corning 175). The levels of hemoglobin and carboxyhemoglobin were measured by the IL-CO-Oximeter 282, the hematocrit by micro-centrifugation, and the 2,3-DPG by an enzymatic method (Sigma-Kit). The oxygen affinity of the whole blood was studied at standard conditions (pH 7.4, temperature 37° C, pCO 40 mm. Hg), with equipment constructed in this laboratory.

In each subject the blood gases were within normal limits and their mean values before and after administration of GTN are identical (Table I): no change was observed for blood gases, hematocrit, hemoglobin, mean corpuscular hemoglobin concentration, or 2,3-DPG as shown by t test for paired data. Table I also gives the mean PO_2 values corresponding to various saturations: they were not influenced by GTN.

Our data clearly demonstrate that high dosages of GTN

[illegible] SD) o[illegible] dissociation curve (n = 7) before and after nitroglycerin at [illegible] p(CO_2 [illegible]) mm Hg T 37 C)

	Control	*After 20 min.*	*After [illegible]*
[illegible]	41 1 (3.5)	40.3 (3.2)	[illegible]
[illegible] Hg)	93.5 (5.5)	92.7 (5.8)	[illegible]
[illegible]	40 1 (1 2)	39 6 (1.6)	[illegible]
[illegible]	4.,3 (2.8)	4.,8 (3.0)	[illegible]
[illegible]	14.6 (1 0)	14.8 (1.1)	[illegible]
[illegible]	32.1 (1 1)	31.8 (1.3)	[illegible]
[illegible] Hb)	11.3 (1.8)	10.1 (2.2)	[illegible]

[illegible]	*PO (mm. Hg) Control*	*PO (mm. Hg) after 20 min.*	*PO (mm. Hg) after [illegible] min.*
[illegible]	9.2 (1 4)	9.0 (1.1)	[illegible]
[illegible]	14.0 (1.7)	14.0 (1 1)	[illegible]
[illegible]	18.2 (1.8)	18.2 (1.2)	[illegible]
[illegible]	22.4 (2.1)	22.2 (1.3)	[illegible]
[illegible]	26.7 (2.6)	26.5 (1.3)	[illegible]
[illegible]	31.6 (2.6)	31 4 (1 4)	[illegible]
[illegible]	38 0 (2.8)	37.6 (1 4)	[illegible]
[illegible]	46 6 (3 2)	46.3 (1.9)	[illegible]
[illegible]	63.4 (5.2)	63 6 (3.2)	[illegible]
91	66.5 (5.6)	68.8 (3 6)	[illegible]
92	70.0 (6.8)	70 9 (4.5)	[illegible]
93	74.2 (7.5)	75 5 (4 8)	[illegible]
94	79 6 (9.1)	81.5 (5 6)	[illegible]
95	86.4 (10.7)	87 7 (6.6)	[illegible]
96	97.2 (13.4)	98.5 (8.9)	[illegible]
97	119.5 (22.0)	113.3 (7.9)	[illegible]
98	141.1 (36 0)	143.4 (12.8)	

Pa CO_2 and O_2 CO_2 and O_2 partial pressure in arterial blood.
SO_2 = Hemoglobin oxygen saturation.
Mean HbCO = around 1 per cent

given sublingually influence neither the slope nor the position of the whole ODC nor the level of 2,3-DPG explicitly this means that high concentration of the drug does not enhance O delivery t the tissues or O captation from the lung. As far as P_{50} is concerned, our data are in concordance with those of Manchester and colleagues[2] ho observed no change in this index five minutes after administration of GTN

Our data, however do not exclude that the ODC mediated O_2 released to the myocardium is modified after GTN

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Stability of NTG

To the Editor

I travenous nitroglycerin (NTG) is being used to control blood pressure during open heart surgery for after [illegible]

ion in patients with heart failure and fo protecting he myocardium. *Due to the lack of vailability of* ercial product, hospital pharmacies are preparing their NTG solutions for intravenous use. Some use stock ons prepared by synthesizing NTG while most prepare solutions from sublingual NTG tablets. The little data this concerning the stability of NTG in intra enous ions is conflicting. Therefore, we conducted study of stability using more specific assay and under more non conditions of use.

e NTG solutions were manufactured by dissolving NTG ngual tablets in sterile water in a large syringe. The *ting NTG solution* was then filtered through 0.22 on filter into sterile vial. This was then further diluted arious concentr*ations to be stored under prescribed condi-* in glass bottles for the duration of the study. Stability of was tested in a 0.1 per cent stock solution with sterile er, in 0.9 per cent sodium chloride, and in 5 per cent trose in water. The NTG solutions were assayed by hod similar to that of Fung and associates. The method is etric assay which involves the alkaline hydrolysis of NTG chromophoric intermediate.

t pre-established times, small amounts of the various dy solutions were withdrawn and analyzed for NTG itent using a Beckman DK2A recording spectrophotome- *Fresh standards of fixed concentrations were prepared* mediately before each analyses and were used to construct andard concentration curve. The various study solutions re then assayed and compared to the standard curv to termine the apparent concentration.

To evaluate the possibility of assay interference from tablet ler tablets containing no NTG were assayed as previously scribed. Under these conditions, there was insignificant sorption at 228 nm, which is in agreement with the work of *ap and colleagues*

The results of the stability of NTG in 0.1 per cent (1 g/ml.) stock solution in water and in 0.9 per cent sodium hloride are summarized in Table I. After three months, there was no significant loss of NTG from the stock solution in 100 ml. glass vial stored in the refrigerator. There was only 1.5 per cent loss in potency at 6 months.

The data for NTG in 5 per cent dextrose in water was difficult to interpret accurately du to assay interference by the dextrose and, therefore, is not reported.

There was no significant loss of NTG from the 200 mcg./ml. concentration in 0.9 per cent chloride intravenous solution in glass bottles after one month. Light or temperature did not seem to affect the stability of NTG in this solution. There was 2.5 to 4.7 per cent loss of potency at three months.

The kinetic assay utilized in this study is simple, accurate, and reasonably free from interference from tablet filler or degradation products of NTG. Other assay techniques, such as the USP assay or Bell's method, measure nitrat and nitrite ions produced by the breakdow of NTG, resulting in a false elevation in the apparent concentration.

Based upon the results of this study we are now routinely preparing a 0.1 per cent stock solution of NTG in sterile water from sublingual tablets. This solution is then used to prepare dilute intravenous solutions for clinical use. Even though our data indicated reasonable stability beyond six months, one month expiration date is placed on the refrigerated stock solution for sterility reasons.

All dilutions (usually 80 to 160 mcg./ml.) prepared for intra enous use are put in 0.9 per cent sodium chloride and assigned 24-hour expiration date. N precautions are used t protect this final solution from light during use. After eight months' experience, physicians in our hospital have noted no significant difference in clinical response between the freshly prepared solution and the stock solution stored for four weeks.

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Table I. Nitroglycerin concentration time data after various experimental conditions

Solution	Conditions			% nitroglycerin remaining in solution				
	Light*	Temp†	Initial concentration	24 hours	1 week	1 month	3 months	6 months
Water	D	R	1000 mcg./ml.	100	100	100	100	98.5
NaCl 0.9%	L	A	200 mcg./ml.	99.1	98.1	98.1	96.8	94.0
NaCl 0.9%	D	R	200 mcg./ml.	100	97.8	97.8	95.3	—

Light: D = Protected from light using Uvibag (Medipak, Inc., Springfield, Ill.); L = exposed to fluorescent light.
†Temperature: R = Refrigerator (4.0° C.); A = Ambient (18-22° C.)

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Book reviews

An Introduction to the Examination of the Cardiovascular System. By A. Leatham, New York, Toronto, 1 University Press, 52 pages. Price $3.25.

This small paperback pocket-size book on exam the cardiovascular system written by an experienced is welcomed. The current over-emphasis on complex instrumentation makes this book even m in training physicians how to examine the heart al made at the bedside. The book is concise the well-selected and illustrated, and the text is lucid Not only undergraduate students but all doctors small pocket-size book worth owning and study

The Mechanics of the Circulation. By C. C. Pedley R. C. Schroter and W. A. Seed, New Y 1978, Oxford University Press, 627 pages. Price $

Much too frequently the circulation is ignored training, clinical practice, and therapeutic heart must be emphasized in the practice of med never to the exclusion of the peripheral circulation. The principles of hydraulics, so important to engineers have important applications to the mechanics of the except that engineers deal with rigid tubes whereas physicians and physiologists deal with distensible tubes. The latter tubing is much more complex. The book is divided in parts, i.e., background mechanics and mechanics of the circulation. The 15 chapters include discussions of the major mechanical principles developed by engineers for rigid tubes and those developed by physiologists and clinicians for the distensible blood vessels. The authors rightfully acknowledge the early and important contributions to fluid mechanics by Thomas Young, physician. He introduced important principles to biology. For example, he introduced the principles of Young' modulus to both physical science and biologic science. The "Law of Laplace was first defined by Young if never by Laplace. This is an extremely valuable book. It provides in single volume wealth of important information, all indispensable to those who employ hemodynamic procedures in physiology and clinical medicine. Surely more extensive study and reading is needed for those who plan to be expert in the mechanics of the circulation.

Pediatric Echocardiography. By Howard P. Gutgesell Paquet, New York, 1978, Harper & Row Publishers, Price $19.95.

of pediatric echocardiography is very good an interesting and rapidly developing subject d ogy. The presentation is good and should be by all pediatricians and cardiologists. The many are excellent. The legends are precise and brief. illustrations are clearly and correctly labelled with few ep ions. There is essentially no text. The only shortcoming the book, as well as of others, is proof of the existence of mic and functional disturbances considered to exist from the echocardiogram. This is illustrated by Figures 2-4 on page Was mitral leaflet prolapse really present? What was the idence and what was its clinical significance? Surely the tracing displays the ECHO pattern. But, did it exist, etc.? All tracings are sharp and clear and well selected. This is an excellent book and is highly recommended to all who interpret echocardiograms.

New Trends in Venous Diseases. Monographs on Standardization of Cardio-angiological Methods. 4. Edited by A. Kappert, Bern, Stuttgart, Vienna, 1977 Hans Huber Publishers, 209 pp. Price Swiss Francs 96.

The eins and venous diseases are not considered sufficiently in the training of physicians and in the practice of medicine. This small book is of considerable importance in providing useful information and in presenting in single volume the prevention of vein diseases and new developments in diseases of eins. The diagnosis and treatment of deep vein thrombosis is clearly discussed in the first chapter. The prevention of deep vein thrombosis, the diagnosis and treatment of pulmonary embolism, dermatologic aspects of chronic enous insufficiency and the pathogenesis of aricose eins are among the topics discussed. Although the book is written for physicians it should interest physiologists as well. The many contributors are European except for one from the USA. The current status is well described in this paperback book based upon a symposium held in Nyon, Switzerland, during November 1976. This is highly recommended and good publication.

Books received

Studies in Acute Heart Failure. By Ronald D Bradley Philadelphia 1977 J B. Lippincott Company 78 pages. Price $0 95

Pain Control i Dentistry By Samuel Seltzer D.D.S., Philadelphia, 1978, J B. Lippincott Company 322 pages. Price $17 00.

Clinical Anatomy of the Heart. By Robert Walmsley and Hamish Watson, forward by John W Kirklin, New York, 1978 Churchill Livingstone, 220 pages. Price $49.50.

Reproductive Endocrinology By Samuel S. C. Yen and Robert B. Jaffe, Philadelphia, 1978, W B. Saunders Compan, 579 pages.

Disorders of the Blood. By R. B. Thompson, M D., F.R.C.P London and New York, 1977 Churchill Livingstone, 6[illegible] pages. Price $60.00.

Announcements

Special course for Physicians

A four-day Course for Practicing Physicians will be held June 18 through 21 at the University f Utah Hospital Medical Center The workshop will emphasize medical management and rehabilitation of alcohol and drug abusers. Lectures, demonstrations, and small group discussions will be included. Attendance is limited. Tuition is $300.00.

Twenty five hours of Category 1 approved credit is offered by the American Academy of Family Physicians. For further information, contact James R Swenson, M.D P.O Box 2604, Salt Lake City Utah 84110.

Physical Sciences and Engineering in Medicine and Biology conference

The nineteenth annual Conference on Physical Sciences and Engineering in Medicine and Biology will be held in Sydney Australia, on August 13 through 17 1979 The conference will be sponsored by the Australasian College of Physical Scientists in Medicine Dr L. A. Geddes, Purdue University West Lafayette, Indiana, U.S A will be the Guest Lecturer A trade exhibition will be held in conjunction with the conference For further information, write Dr R. W Gill, Organizing Secretary P O Box 1099, Royal Exchange, N.S.W Australia 2000

Ultrasound in Medicine

The American Institute of Ultrasound in Medicine will hold its twenty fourth annual meeting in conjunction with the annual meeting of the America Societ of Ultrasound Technical Specialists, in Montreal, Quebec C nada, on August 27 through 31, 1979. The Planning Committee is working o[n a] superb scientific session as well as scientific exhibits, p[…] sessions, and one of the largest ultrasound instrumentat[ion] exhibits in the western hemisphere. For further informat[ion] contact. AIUM/ASUTS Montreal 79, 6161 N. May A[…] Suit 270, Oklahoma City Okla. 73112. Telephone (4[…] 840-3721.

International Congress of Therapeutics

The XVth International Congress of Therapeutics wi[ll be] held in Brussels, Belgium, from September 5 through 8, 19[…] under the sponsorship of the International Union of The[ra]peutics. Main congress topics will include new advances in […] treatment of coronary diseases, hypothyroid conditions, […] depressive illness. For further information, contact: Secre[…] let, XVth International Congress of Therapeutics, Dep[art]ment of Cardiology Hôpital Universitaire Saint-Pierre, […] Brussels, Belgium.

Postgraduate Symposium on Pediatric Cardiology 1979

The Postgraduate Symposium on Paediatric Cardiol[ogy] 1979 will be held in Amsterdam, The Netherlands, on Sep[tem]ber 5 through 7 1979. The symposium is being sponsored [by] the Interuniversity Cardiology Institute of Amsterdam. T[…] ty speakers will be featured in six main sessions. Registra[tion] fee, including lunches, is 550 guilders. For further informa[tion] contact. Consultants and Organizers, ICI Paediatric Card[iol]ogy 1979 P.O. Box 71073, 1008 BC Amsterdam, The Net[her]lands.

American Heart Journal

An international publication for the study of the circulation

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